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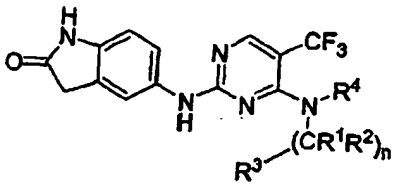
(54) Title: PYRIMIDINE DERIVATIVES FOR THE TREATMENT OF ABNORMAL CELL GROWTH



(I)

(57) Abstract: The present invention relates to a compound of the formula (I), wherein $R^1$-$R^4$ are as defined herein. Such novel pyrimidine derivatives are useful in thetreatment of abnormal cell growth, such as cancer, in mammals. This invention also relates to a method of using such compounds in the treatment of abnormal cell growth in mammals, especially humans, and to pharmaceutical compositions containing such compounds.

# PYRIMIDINE DERIVATIVES FOR THE TREATMENT OF ABNORMAL CELL GROWTH

## Background of the Invention

This invention relates to novel pyrimidine derivatives that are useful in the treatment of abnormal cell growth, such as cancer, in mammals. This invention also relates to a method of using such compounds in the treatment of abnormal cell growth in mammals, especially humans, and to pharmaceutical compositions containing such compounds.

It is known that a cell may become cancerous by virtue of the transformation of a portion of its DNA into an oncogene (i.e., a gene which, on activation, leads to the formation of malignant tumor cells). Many oncogenes encode proteins that are aberrant tyrosine kinases capable of causing cell transformation. Alternatively, the overexpression of a normal proto-oncogenic tyrosine kinase may also result in proliferative disorders, sometimes resulting in a malignant phenotype.

Receptor tyrosine kinases are enzymes which span the cell membrane and possess an extracellular binding domain for growth factors such as epidermal growth factor, a transmembrane domain, and an intracellular portion which functions as a kinase to phosphorylate specific tyrosine residues in proteins and hence to influence cell proliferation. Other receptor tyrosine kinases include c-erbB-2, c-met, tie-2, PDGFr, FGFr, and VEGFR. It is known that such kinases are frequently aberrantly expressed in common human cancers such as breast cancer, gastrointestinal cancer such as colon, rectal or stomach cancer, leukemia, and ovarian, bronchial or pancreatic cancer. It has also been shown that epidermal growth factor receptor (EGFR), which possesses tyrosine kinase activity, is mutated and/or overexpressed in many human cancers such as brain, lung, squamous cell, bladder, gastric, breast, head and neck, oesophageal, gynecological and thyroid tumors.

Accordingly, it has been recognized that inhibitors of receptor tyrosine kinases are useful as selective inhibitors of the growth of mammalian cancer cells. For example, erbstatin, a tyrosine kinase inhibitor, selectively attenuates the growth in athymic nude mice of a transplanted human mammary carcinoma that expresses epidermal growth factor receptor tyrosine kinase (EGFR) but is without effect on the growth of another carcinoma that does not express the EGF receptor. Thus, selective inhibitors of certain receptor tyrosine kinases, are useful in the treatment of abnormal cell growth, in particular cancer, in mammals. In addition to receptor tyrosine kinses, selective inhibitors of certain non-receptor tyrosine kinases, such as FAK (focal adhesion kinase), lck, src, abl or serine/threonine kinases (e.g.: cyclin dependent

kinases, are useful in the treatment of abnormal cell growth, in particular cancer, in mammals. FAK is also known as the Protein-Tyrosine Kinase 2, PTK2.

Convincing evidence suggests that FAK, a cytoplasmic, non-receptor tyrosine kinase, plays an essential role in cell-matrix signal transduction pathways (Clark and Brugge 1995, Science 268: 233-239) and its aberrant activation is associated with an increase in the metastatic potential of tumors (Owens et al. 1995, Cancer Research 55: 2752-2755). FAK was originally identified as a 125 kDa protein highly tyrosine-phosphorylated in cells transformed by v-Src. FAK was subsequently found to be a tyrosine kinase that localizes to focal adhesions, which are contact points between cultured cells and their underlying substratum and sites of intense tyrosine phosphorylation. FAK is phosphorylated and, thus, activated in response to extracellular matrix (ECM)-binding to integrins. Recently, studies have demonstrated that an increase in FAK mRNA levels accompanied invasive transformation of tumors and attenuation of the expression of FAK (through the use of antisense oligonucleotides) induces apoptosis in tumor cells (Xu et al. 1996, Cell Growth and Diff. 7: 413-418). In addition to being expressed in most tissue types, FAK is found at elevated levels in most human cancers, particularly in highly invasive metastases.

Various compounds, such as styrene derivatives, have also been shown to possess tyrosine kinase inhibitory properties. Five European patent publications, namely EP 0 566 226 A1 (published October 20, 1993), EP 0 602 851 A1 (published June 22, 1994), EP 0 635 507 A1 (published January 25, 1995), EP 0 635 498 A1 (published January 25, 1995), and EP 0 520 722 A1 (published December 30, 1992), refer to certain bicyclic derivatives, in particular quinazoline derivatives, as possessing anti-cancer properties that result from their tyrosine kinase inhibitory properties.

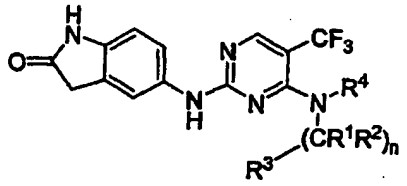
Also, World Patent Application WO 92/20642 (published November 26, 1992), refers to certain bis-mono and bicyclic aryl and heteroaryl compounds as tyrosine kinase inhibitors that are useful in inhibiting abnormal cell proliferation. World Patent Applications WO96/16960 (published June 6, 1996), WO 96/09294 (published March 6, 1996), WO 97/30034 (published August 21, 1997), WO 98/02434 (published January 22, 1998), WO 98/02437 (published January 22, 1998), and WO 98/02438 (published January 22, 1998), also refer to substituted bicyclic heteroaromatic derivatives as tyrosine kinase inhibitors that are useful for the same purpose.

U.S. Patent Application Serial No. 60/435,670, filed December 20, 2002 (Attorney Docket No. PC25339) relates to a broad class of novel pyrimidine derivatives that are selective inhibitors of FAK. As such, these compounds are useful in the treatment of abnormal cell growth.

Accordingly, a need exists for additional selective inhibitors of certain receptor and non-receptor tyrosine kinases, useful in the treatment of abnormal cell growth, such as cancer, in mammals. The present invention provides for novel pyrimidine derivatives that are selective inhibitors of the non-receptor tyrosine kinase, FAK, and are useful in the treatment of abnormal cell growth.

## Summary of the Invention

The present invention relates to a compound of the formula 1



1

or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof,

wherein n is an integer from 1 to 3;

each $R^1$ is a substituent independently selected from the group consisting of hydrogen, hydroxy, -($C_1$-$C_6$)alkyl, -($C_3$-$C_7$)cycloalkyl, -($C_2$-$C_9$)heterocyclyl, -O($C_1$-$C_6$)alkyl, -O($C_3$-$C_7$)cycloalkyl, -O($C_2$-$C_9$)heterocyclyl, -$NR^5R^6$, -$SR^7$, -$SOR^7$, -$SO_2R^7$, -$CO_2R^5$, -$CONR^5R^6$, -$SO_2NR^5R^6$, -NHCOR$^5$, -$NR^5CONR^5R^6$, and -$NR^5SO_2R^7$; with the proviso that a heteroatom of the foregoing $R^1$ substituents may not be bound to an $sp^3$ carbon atom bound to another heteroatom; and said $R^1$ substituents, -($C_1$-$C_6$)alkyl, -($C_3$-$C_7$)cycloalkyl, -($C_2$-$C_9$)heterocyclyl, -O($C_1$-$C_6$)alkyl, -O($C_3$-$C_7$)cycloalkyl, -O($C_2$-$C_9$)heterocyclyl, -$NR^5R^6$, -$SR^7$, -$SOR^7$, -$SO_2R^7$, -$CO_2R^5$, -$CONR^5R^6$, - $SO_2NR^5R^6$, -NHCOR$^5$, -$NR^5CONR^5R^6$, and -$NR^5SO_2R^7$ groups are optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -$CF_3$, -CN, -($C_1$-$C_6$)alkyl, -$NR^5R^6$, -$OR^5$, -($C_3$-$C_7$)cycloalkyl, -($C_2$-$C_9$)heterocyclyl, -$CO_2R^5$, -$CONR^5R^6$ and-$CONR^5R^6$; with the proviso that a heteroatom of the foregoing optional $R^1$ moieties may not be bound to an $sp^3$ carbon atom bound to another heteroatom;

each $R^2$ is a substituent independently selected from the group consisting of hydrogen, -($C_1$-$C_6$)alkyl, -($C_2$-$C_6$)alkenyl, -($C_2$-$C_6$)alkynyl, -($C_3$-$C_7$)cycloalkyl, -($C_2$-$C_9$)heterocyclyl, -$CO_2R^5$, and -$CONR^5R^6$; with the proviso that a heteroatom of any of the foregoing $R^2$ substituents may not be bound to an $sp^3$ carbon atom that is bound to another heteroatom; and said $R^2$ substituents, -($C_1$-$C_6$)alkyl, -($C_2$-$C_6$)alkenyl, -($C_2$-$C_6$)alkynyl, -($C_3$-$C_7$)cycloalkyl, -($C_2$-$C_9$)heterocyclyl, -$CO_2R^5$, and -$CONR^5R^6$, are optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -$CF_3$, -$NO_2$, -CN, -($C_1$-$C_6$)alkyl, -($C_2$-$C_6$)alkenyl, -($C_2$-$C_6$)alkynyl, -C=N-OH, -C=N-

O((C1-C6)alkyl), -NR5R6, -OR5, -(C3-C7)cycloalkyl, -(C2-C9)heterocyclyl, -CO2R5, -CONR5R6, -CONR5R6, -SR7, -SOR7, -SO2R7, -SO2NR5R6, -NHCOR5, -NR5CONR5R6, and -NR5SO2R7, wherein said –(C2-C6)alkenyl and –(C2-C6)alkynyl R2 moieties may be optionally substituted by one to three R5 groups; and with the proviso that a heteroatom of the foregoing optional R2 moieties may not be bound to an sp3 carbon atom bound to another heteroatom;

R1 and R2 may be taken together with the atom(s) to which they are attached to form a cyclic group, -(C3-C10)cycloalkyl or -(C2-C9)heterocyclyl, wherein said cyclic group is optionally substituted by one to three moieties selected from the group consisting of hydrogen, halogen, hydroxy, -CF3, -NO2, -CN, -(C1-C6)alkyl, -(C2-C6)alkenyl, -(C2-C6)alkynyl, -C=N-OH, -C=N-O((C1-C6)alkyl), -NR5R6, -OR5, -(C3-C7)cycloalkyl, -(C2-C9)heterocyclyl, -CO2R5, -CONR5R6, -CONR5R6, -SR7, -SOR7, -SO2R7, -SO2NR5R6, -NHCOR5, -NR5CONR5R6, and -NR5SO2R7, wherein said –(C2-C6)alkenyl and –(C2-C6)alkynyl moieties of said cyclic group may be optionally substituted by one to three R6 groups, and said cyclic group is optionally interrupted by one to three elements selected from the group consisting of –(C=O), -SO2, -S-, -O-, -N-, -NH- and –NR6, with the proviso that any of the foregoing cyclic group moieties or elements may not be bound to an sp3 carbon atom that is bound to another heteroatom;

R3 is a suitable substituent, including, but not limited to a substituent selected from the group consisting of:

(a) hydrogen;

(b) -(C6-C10)aryl or -(C1-C9)heteroaryl, optionally substituted by one to three moieties independently selected from the group consisting of halogen, hydroxy, -(C1-C6)alkyl, -(C1-C6)alkyl-P(O)(O(C1-C6)alkyl)2, -(C3-C10)cycloalkyl, (C6-C10)aryl, (C2-C9)heterocyclyl, -(C1-C9)heteroaryl, -NR5R6, -NHSO2(C1-C6)alkyl, -NHSO2(C3-C6)cycloalkyl, -N((C1-C6)alkyl)(SO2-C1-C6)alkyl), -N((C1-C6)alkyl)(SO2(C3-C6)cycloalkyl), -O(C1-C6)alkyl, -O-SO2(C1-C6)alkyl, -(CO)(C1-C6)alkyl, -(CO)CF3, -(CO)(C3-C10)cycloalkyl, -(CO)(C6-C10)aryl, -(CO)(C2-C9)heterocyclyl, -(CO)(C1-C9)heteroaryl, -(CO)O(C1-C6)alkyl, -(CO)O(C3-C10)cycloalkyl, -(CO)O(C6-C10)aryl, -(CO)O(C2-C9)heterocyclyl, -(CO)O(C1-C9)heteroaryl, -(CO)(C1-C6)alkyl-O(C1-C6)alkyl, -SO2(C1-C6)alkyl, -SO2(C3-C6)cycloalkyl, SO2CF3, SO2NH2, SO2NH(C1-C6)alkyl, -SO2NH(C3-C6)cycloalkyl, -SO2N((C1-C6)alkyl)2, -SO2N((C3-C6)cycloalkyl)2, -SO2NR5R6, and -SO2N(C1-C6)alkyl-(C6-C10)aryl; wherein said -(C6-C10) aryl or -(C1-C9) heteroaryl are optionally interrupted by one to three elements selected from the group consisting of –(C=O), -SO2, -S-, -O-, -N-, -NH- and –NR5; and R5 and R6 of said NR5R6 R3(b) group may be taken together with the atoms to which they are attached to form a -(C2-C9)heterocyclyl;

(c) -($C_3$-$C_{10}$)cycloalkyl, -($C_2$-$C_9$)heterocyclyl, and -($C_1$-$C_6$)alkyl-($C_2$-$C_9$) heterocyclyl, optionally substituted by one to three moieties independently selected from the group consisting of halogen, hydroxy, -($C_1$-$C_6$)alkyl, -($C_1$-$C_6$)alkyl-P(O)(O($C_1$-$C_6$)alkyl)$_2$, -($C_3$-$C_{10}$)cycloalkyl, ($C_6$-$C_{10}$)aryl, ($C_2$-$C_9$)heterocyclyl, -($C_1$-$C_9$)heteroaryl, -$NR^5R^6$, -$NSO_2$($C_1$-$C_6$)alkyl, -$NHSO_2$($C_3$-$C_6$)cycloalkyl, -N(($C_1$-$C_6$)alkyl)($SO_2$-$C_1$-$C_6$)alkyl), -N(($C_1$-$C_6$)alkyl)($SO_2$($C_3$-$C_6$)cycloalkyl), -O($C_1$-$C_6$)alkyl, -O-$SO_2$($C_1$-$C_6$)alkyl, -O-$SO_2$($C_1$-$C_6$)alkyl, -(CO)($C_1$-$C_6$)alkyl, -(CO)$CF_3$, -(CO)($C_3$-$C_{10}$)cycloalkyl, -(CO)($C_6$-$C_{10}$)aryl, -(CO)($C_2$-$C_9$)heterocyclyl, -(CO)($C_1$-$C_9$)heteroaryl, -(CO)O($C_1$-$C_6$)alkyl, -(CO)O($C_3$-$C_{10}$)cycloalkyl, -(CO)O($C_6$-$C_{10}$)aryl, -(CO)O($C_2$-$C_9$)heterocyclyl, -(CO)O($C_1$-$C_9$)heteroaryl, -(CO)($C_1$-$C_6$)alkyl-O($C_1$-$C_6$)alkyl, -$SO_2$($C_1$-$C_6$)alkyl, -$SO_2$($C_3$-$C_6$)cycloalkyl, $SO_2CF_3$, $SO_2NH_2$, $SO_2NH$($C_1$-$C_6$)alkyl, -$SO_2NH$($C_3$-$C_6$)cycloalkyl, -$SO_2N$(($C_1$-$C_6$)alkyl)$_2$, -$SO_2N$(($C_3$-$C_6$)cycloalkyl)$_2$, -$SO_2NR^5R^6$, and -$SO_2N$($C_1$-$C_6$)alkyl-($C_6$-$C_{10}$)aryl; wherein said -($C_3$-$C_{10}$)cycloalkyl, -($C_2$-$C_9$)heterocyclyl, and -($C_1$-$C_6$)alkyl-($C_2$-$C_9$) heterocyclyl are optionally interrupted by one to three elements selected from the group consisting of –(C=O), -$SO_2$, -S-, -O-, -N-, -NH- and –$NR^5$; and $R^5$ and $R^6$ of said $NR^5R^6$ $R^3$(b) group may be taken together with the atoms to which they are attached to form a -($C_2$-$C_9$)heterocyclyl;

(d) -($C_1$-$C_6$)alkyl optionally substituted by one to three moieties selected from the group consisting of halogen, hydroxy, -($C_1$-$C_6$)alkyl, -($C_1$-$C_6$)alkyl-P(O)(O($C_1$-$C_6$)alkyl)$_2$, -($C_3$-$C_{10}$)cycloalkyl, ($C_6$-$C_{10}$)aryl, ($C_2$-$C_9$)heterocyclyl, -($C_1$-$C_9$)heteroaryl, -$NR^5R^6$, -$NSO_2$($C_1$-$C_6$)alkyl, -$NHSO_2$($C_3$-$C_6$)cycloalkyl, -N(($C_1$-$C_6$)alkyl)($SO_2$-$C_1$-$C_6$)alkyl), -N(($C_1$-$C_6$)alkyl)($SO_2$($C_3$-$C_6$)cycloalkyl), -O($C_1$-$C_6$)alkyl, -O-$SO_2$($C_1$-$C_6$)alkyl, -(CO)($C_1$-$C_6$)alkyl, -(CO)$CF_3$, -(CO)($C_3$-$C_{10}$)cycloalkyl, -(CO)($C_6$-$C_{10}$)aryl, -(CO)($C_2$-$C_9$)heterocyclyl, -(CO)($C_1$-$C_9$)heteroaryl, -(CO)O($C_1$-$C_6$)alkyl, -(CO)O($C_3$-$C_{10}$)cycloalkyl, -(CO)O($C_6$-$C_{10}$)aryl, -(CO)O($C_2$-$C_9$)heterocyclyl, -(CO)O($C_1$-$C_9$)heteroaryl, -(CO)($C_1$-$C_6$)alkyl-O($C_1$-$C_6$)alkyl, -$SO_2$($C_1$-$C_6$)alkyl, -$SO_2$($C_3$-$C_6$)cycloalkyl, $SO_2CF_3$, $SO_2NH_2$, $SO_2NH$($C_1$-$C_6$)alkyl, -$SO_2NH$($C_3$-$C_6$)cycloalkyl, -$SO_2N$(($C_1$-$C_6$)alkyl)$_2$, -$SO_2N$(($C_3$-$C_6$)cycloalkyl)$_2$, -$SO_2NR^5R^6$, and -$SO_2N$($C_1$-$C_6$)alkyl-($C_6$-$C_{10}$)aryl; wherein said -($C_1$-$C_6$)alkyl is optionally interrupted by one to three elements selected from the group consisting of –(C=O), -$SO_2$, -S-, -O-, -N-, -NH- and -$NR^5$; and $R^5$ and $R^6$ of said $NR^5R^6$ $R^3$(b) group may be taken together with the atoms to which they are attached to form a -($C_2$-$C_9$)heterocyclyl;

and wherein each $R^3$ (b)-(d) substituent, moiety, or element is optionally substituted by one to three radicals independently selected from the group consisting of hydrogen, halogen, hydroxy, -$CF_3$, -$NO_2$, -CN, -($C_1$-$C_6$)alkyl, -($C_2$-$C_6$)alkenyl, -($C_2$-$C_6$)alkynyl, -($C_3$-$C_7$)cycloalkyl, -($C_2$-$C_9$)heterocyclyl, -($C_6$-$C_{10}$)aryl, -($C_1$-$C_9$)heteroaryl, -O($C_1$-$C_6$)alkyl, -O($C_3$-$C_7$)cycloalkyl, -O($C_2$-$C_9$)heterocyclyl, -C=N-OH, -C=N-O($C_1$-$C_6$ alkyl), -$NR^5R^6$, -$SR^7$,

-$SOR^7$, -$SO_2R^7$, -$CO_2R^5$, -$CONR^5R^6$, -$SO_2NR^5R^6$, -NHCOR$^5$, -$NR^5CONR^5R^6$, and -$NR^5SO_2R^7$; with the proviso that a heteroatom of the foregoing $R^3$ (b)-(d) substituents, moieties, elements or radicals may not be bound to an $sp^3$ carbon atom bound to another heteroatom; and wherein $R^5$ and $R^6$ of said -$NR^5R^6$, -$CONR^5R^6$, -$SO_2NR^5R^6$, and -$NR^5CONR^5R^6$ groups may be taken together with the atoms to which they are attached to form a -($C_2$-$C_9$)heterocyclyl;

$R^4$ is a substituent selected from the group consisting of hydrogen, ($C_1$-$C_6$)alkyl, -($C_3$-$C_7$)cycloalkyl, and -($C_2$-$C_9$)heterocyclyl; wherein said ($C_1$-$C_6$)alkyl, -($C_3$-$C_7$)cycloalkyl, and -($C_2$-$C_9$)heterocyclyl $R^4$ substituents are optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, -($C_1$-$C_6$)alkyl, -CN, -$NR^5_2$, -$OR^5$, -($C_3$-$C_7$)cycloalkyl, -($C_2$-$C_9$)heterocyclyl, -$CO_2R^5$, and -$CONR^5R^6$; with the proviso that a heteroatom of the foregoing $R^4$ substituents may not be bound to an $sp^3$ carbon atom bound to another heteroatom; and wherein $R^5$ and $R^6$ of said -$CONR^5R^6$ group may be taken together with the atoms to which they are attached to form a -($C_3$-$C_{10}$)cycloalkyl or -($C_2$-$C_9$)heterocyclyl;

$R^5$ and $R^6$ are each substituents independently selected from the group consisting of hydrogen, -($C_1$-$C_6$)alkyl, -($C_3$-$C_7$)cycloalkyl, -($C_2$-$C_9$)heterocyclyl, -($C_6$-$C_{10}$)aryl, and -($C_1$-$C_9$)heteroaryl; wherein said -($C_1$-$C_6$)alkyl, -($C_3$-$C_7$)cycloalkyl, -($C_2$-$C_9$)heterocyclyl, -($C_6$-$C_{10}$)aryl, and -($C_1$-$C_9$)heteroaryl $R^5$ or $R^6$ substituents are optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, -$CF_3$, -CN, -($C_1$-$C_6$)alkyl, -NH($C_1$-$C_6$)alkyl, -NH($C_3$-$C_7$)cycloalkyl, -NH($C_2$-$C_9$)heterocyclyl, -NH($C_6$-$C_{10}$)aryl, -NH($C_1$-$C_9$)heteroaryl, -N(($C_1$-$C_6$)alkyl)$_2$, -N(($C_3$-$C_7$)cycloalkyl)$_2$, -N(($C_2$-$C_9$)heterocyclyl)$_2$, -N(($C_6$-$C_{10}$)aryl)$_2$, -N(($C_1$-$C_9$)heteroaryl)$_2$, -O($C_1$-$C_6$)alkyl, -O($C_3$-$C_7$)cycloalkyl, -O($C_2$-$C_9$)heterocyclyl, -O($C_6$-$C_{10}$)aryl, -O($C_1$-$C_9$)heteroaryl, -($C_3$-$C_7$)cycloalkyl, -($C_2$-$C_9$)heterocyclyl, -$CO_2R^7$, -$CONH_2$, -$CONHR^7$, and -$CONR^7R^8$; with the proviso that a heteroatom of the foregoing $R^5$ or $R^6$ substituents or moieties may not be bound to an $sp^3$ carbon atom bound to another heteroatoms; and wherein $R^7$ and $R^8$ of said -$CONR^7R^8$ group may be taken together with the atoms to which they are attached to form a –($C_1$-$C_9$) heteroaryl;

$R^5$ and $R^6$ may be taken together with the atom(s) to which they are attached to form a cyclic group, -($C_3$-$C_{10}$)cycloalkyl or -($C_2$-$C_9$)heterocyclyl, wherein said cyclic group is optionally substituted by one to three moieties selected from the group consisting of hydrogen, halogen, hydroxy, -$CF_3$, -$NO_2$, -CN, -($C_1$-$C_6$)alkyl, -($C_2$-$C_6$)alkenyl, -($C_2$-$C_6$)alkynyl, -C=N-OH, -C=N-O(($C_1$-$C_6$)alkyl), -$NR^5R^6$, -$OR^5$, -($C_3$-$C_7$)cycloalkyl, -($C_2$-$C_9$)heterocyclyl, -$CO_2R^5$, -$CONR^5R^6$, -$CONR^5R^8$, -$SR^7$, -$SOR^7$, -$SO_2R^7$, -$SO_2NR^5R^6$, -NHCOR$^5$, -$NR^5CONR^5R^6$, and -$NR^5SO_2R^7$, wherein said –($C_2$-$C_6$)alkenyl and –($C_2$-$C_6$)alkynyl moieties of said cyclic group may be optionally substituted by one to three $R^7$ groups, and said cyclic group is

optionally interrupted by one to three elements selected from the group consisting of –(C=O), $-SO_2$, -S-, -O-, -N-, -NH- and $-NR^5$, with the proviso that any of the foregoing cyclic group moieties or elements may not be bound to an $sp^3$ carbon atom that is bound to another heteroatom;

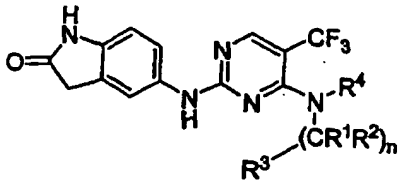
$R^7$ is a substituent selected from the group consisting of $-(C_1-C_6)$alkyl, $-(C_3-C_7)$cycloalkyl, $-(C_2-C_9)$heterocyclyl, $-(C_6-C_{10})$aryl, and $-(C_1-C_9)$ heteroaryl; wherein said $-(C_1-C_6)$alkyl, $-(C_3-C_7)$cycloalkyl, $-(C_2-C_9)$heterocyclyl, $-(C_6-C_{10})$aryl, and $-(C_1-C_9)$ heteroaryl $R^7$ substituents are optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, $-(C_1-C_6)$alkyl, $-NR^8_2$, and $-O(C_1-C_6)$alkyl, with the proviso that a heteroatom of the foregoing $R^7$ substituents or moieties may not be bound to an $sp^3$ carbon atom bound to another heteroatom;

$R^8$ is a substituent selected from the group consisting of hydrogen, $-(C_1-C_6)$alkyl, $-(C_3-C_7)$cycloalkyl, $-(C_2-C_9)$heterocyclyl, $-(C_6-C_{10})$aryl, and $-(C_1-C_9)$ heteroaryl; wherein said $-(C_1-C_6)$alkyl, $-(C_3-C_7)$cycloalkyl, $-(C_2-C_9)$heterocyclyl, $-(C_6-C_{10})$aryl, and $-(C_1-C_9)$ heteroaryl $R^8$ radicals are optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, $-(C_1-C_6)$alkyl, $-NH_2$, $-NHR^9$, $-NR^9_2$, $OR^9$, $-(C_3-C_7)$cycloalkyl, $-(C_2-C_9)$heterocyclyl, $-CO_2R^{10}$, $-CONH_2$, $-CONHR^{10}$, and $-CONR^{10}R^{11}$; with the proviso that a heteroatom of the foregoing $R^8$ substituents or moieties may not be bound to an $sp^3$ carbon atom bound to another heteroatom; and wherein $R^{10}$ and $R^{11}$ of $-CONR^{10}R^{11}$ may be taken together with the atoms to which they are attached to form a -(C2-$C_9$)heterocyclyl;

$R^9$ and $R^{10}$ are each $-(C_1-C_6)$alkyl and may be taken together with the atoms to which they are attached to form a $-(C_2-C_9)$heterocyclyl; and

$R^{11}$ is hydrogen or $-(C_1-C_6)$alkyl.

In a preferred embodiment, the present invention relates to a compound of the formula 1



1

or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof,

wherein n is an integer from 1 to 3;

each $R^1$ is a substituent independently selected from the group consisting of hydrogen, hydroxy, $-(C_1-C_6)$alkyl, $-(C_3-C_7)$cycloalkyl, $-(C_2-C_9)$heterocyclyl, $-O(C_1-C_6)$alkyl, -

$O(C_3-C_7)$cycloalkyl, $-O(C_2-C_9)$heterocyclyl, $-NR^5R^6$, $-SR^7$, $-SOR^7$, $-SO_2R^7$, $-CO_2R^5$, $-CONR^5R^6$, $-SO_2NR^5R^6$, $-NHCOR^5$, $-NR^5CONR^5R^6$, and $-NR^5SO_2R^7$; with the proviso that a heteroatom of the foregoing $R^1$ substituents may not be bound to an $sp^3$ carbon atom bound to another heteroatom; and said $R^1$ substituents, $-(C_1-C_6)$alkyl, $-(C_3-C_7)$cycloalkyl, $-(C_2-C_9)$heterocyclyl, $-O(C_1-C_6)$alkyl, $-O(C_3-C_7)$cycloalkyl, $-O(C_2-C_9)$heterocyclyl, $-NR^5R^6$, $-SR^7$, $-SOR^7$, $-SO_2R^7$, $-CO_2R^5$, $-CONR^5R^6$, $-SO_2NR^5R^6$, $-NHCOR^5$, $-NR^5CONR^5R^6$, and $-NR^5SO_2R^7$ groups are optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, $-CF_3$, -CN, $-(C_1-C_6)$alkyl, $-NR^5R^6$, $-OR^5$, $-(C_3-C_7)$cycloalkyl, $-(C_2-C_9)$heterocyclyl, $-CO_2R^5$, $-CONR^5R^6$ and-$CONR^5R^5$; with the proviso that a heteroatom of the foregoing optional $R^1$ moieties may not be bound to an $sp^3$ carbon atom bound to another heteroatom;

each $R^2$ is a substituent independently selected from the group consisting of hydrogen, $-(C_1-C_6)$alkyl, $-(C_2-C_6)$alkenyl, $-(C_2-C_6)$alkynyl, $-(C_3-C_7)$cycloalkyl, $-(C_2-C_9)$heterocyclyl, $-CO_2R^5$, and $-CONR^5R^6$; with the proviso that a heteroatom of any of the foregoing $R^2$ substituents may not be bound to an $sp^3$ carbon atom that is bound to another heteroatom; and said $R^2$ substituents, $-(C_1-C_6)$alkyl, $-(C_2-C_6)$alkenyl, $-(C_2-C_6)$alkynyl, $-(C_3-C_7)$cycloalkyl, $-(C_2-C_9)$heterocyclyl, $-CO_2R^5$, and $-CONR^5R^6$, are optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, $-CF_3$, $-NO_2$, -CN, $-(C_1-C_6)$alkyl, $-(C_2-C_6)$alkenyl, $-(C_2-C_6)$alkynyl, -C=N-OH, -C=N-$O((C_1-C_6)$alkyl), $-NR^5R^6$, $-OR^5$, $-(C_3-C_7)$cycloalkyl, $-(C_2-C_9)$heterocyclyl, $-CO_2R^5$, $-CONR^5R^6$, $-CONR^5R^6$, $-SR^7$, $-SOR^7$, $-SO_2R^7$, $-SO_2NR^5R^6$, $-NHCOR^5$, $-NR^5CONR^5R^6$, and $-NR^5SO_2R^7$, wherein said $-(C_2-C_6)$alkenyl and $-(C_2-C_6)$alkynyl $R^2$ moieties may be optionally substituted by one to three $R^5$ groups; and with the proviso that a heteroatom of the foregoing optional $R^2$ moieties may not be bound to an $sp^3$ carbon atom bound to another heteroatom;

$R^1$ and $R^2$ may be taken together with the atom(s) to which they are attached to form a cyclic group, $-(C_3-C_{10})$cycloalkyl or $-(C_2-C_9)$heterocyclyl, wherein said cyclic group is optionally substituted by one to three moieties selected from the group consisting of hydrogen, halogen, hydroxy, $-CF_3$, $-NO_2$, -CN, $-(C_1-C_6)$alkyl, $-(C_2-C_6)$alkenyl, $-(C_2-C_6)$alkynyl, -C=N-OH, -C=N-$O((C_1-C_6)$alkyl), $-NR^5R^6$, $-OR^5$, $-(C_3-C_7)$cycloalkyl, $-(C_2-C_9)$heterocyclyl, $-CO_2R^5$, $-CONR^5R^6$, $-CONR^5R^6$, $-SR^7$, $-SOR^7$, $-SO_2R^7$, $-SO_2NR^5R^6$, $-NHCOR^5$, $-NR^5CONR^5R^6$, and $-NR^5SO_2R^7$, wherein said $-(C_2-C_6)$alkenyl and $-(C_2-C_6)$alkynyl moieties of said cyclic group may be optionally substituted by one to three $R^5$ groups, and said cyclic group is optionally interrupted by one to three elements selected from the group consisting of -(C=O), $-SO_2$, -S-, -O-, -N-, -NH- and $-NR^5$, with the proviso that any of the foregoing cyclic group moieties or elements may not be bound to an $sp^3$ carbon atom that is bound to another heteroatom;

$R^3$ is a substituent selected from the group consisting of:

(a) hydrogen;

(b) -($C_6$-$C_{10}$)aryl or -($C_1$-$C_9$)heteroaryl, optionally substituted by one to three moieties independently selected from the group consisting of halogen, hydroxy, -($C_1$-$C_6$)alkyl, -($C_1$-$C_6$)alkyl-P(O)(O($C_1$-$C_6$)alkyl)$_2$, -($C_3$-$C_{10}$)cycloalkyl, ($C_6$-$C_{10}$)aryl, ($C_2$-$C_9$)heterocyclyl, -($C_1$-$C_9$)heteroaryl, -$NR^5R^6$, -$NHSO_2$($C_1$-$C_6$)alkyl, -$NHSO_2$($C_3$-$C_6$)cycloalkyl, -N(($C_1$-$C_6$)alkyl)($SO_2$-$C_1$-$C_6$)alkyl), -N(($C_1$-$C_6$)alkyl)($SO_2$($C_3$-$C_6$)cycloalkyl), -O($C_1$-$C_6$)alkyl, -O-$SO_2$($C_1$-$C_6$)alkyl, -(CO)($C_1$-$C_6$)alkyl, -(CO)$CF_3$, -(CO)($C_3$-$C_{10}$)cycloalkyl, -(CO)($C_6$-$C_{10}$)aryl, -(CO)($C_2$-$C_9$)heterocyclyl, -(CO)($C_1$-$C_9$)heteroaryl, -(CO)O($C_1$-$C_6$)alkyl, -(CO)O($C_3$-$C_{10}$)cycloalkyl, -(CO)O($C_6$-$C_{10}$)aryl, -(CO)O($C_2$-$C_9$)heterocyclyl, -(CO)O($C_1$-$C_9$)heteroaryl, -(CO)($C_1$-$C_6$)alkyl-O($C_1$-$C_6$)alkyl, -$SO_2$($C_1$-$C_6$)alkyl, -$SO_2$($C_3$-$C_6$)cycloalkyl, $SO_2CF_3$, $SO_2NH_2$, $SO_2NH$($C_1$-$C_6$)alkyl, -$SO_2NH$($C_3$-$C_6$)cycloalkyl, -$SO_2N$(($C_1$-$C_6$)alkyl)$_2$, -$SO_2N$(($C_3$-$C_6$)cycloalkyl)$_2$, -$SO_2NR^5R^6$, and -$SO_2N$($C_1$-$C_6$)alkyl-($C_6$-$C_{10}$)aryl; wherein said -($C_6$-$C_{10}$) aryl or -($C_1$-$C_9$) heteroaryl are optionally interrupted by one to three elements selected from the group consisting of –(C=O), -$SO_2$, -S-,–O-, -N-, -NH- and –$NR^5$; and $R^5$ and $R^6$ of said $NR^5R^6$ $R^3$(b) group may be taken together with the atoms to which they are attached to form a -($C_2$-$C_9$)heterocyclyl;

(c) -($C_3$-$C_{10}$)cycloalkyl, -($C_2$-$C_9$)heterocyclyl, and -($C_1$-$C_6$)alkyl-($C_2$-$C_9$) heterocyclyl, optionally substituted by one to three moieties independently selected from the group consisting of halogen, hydroxy, -($C_1$-$C_6$)alkyl, -($C_1$-$C_6$)alkyl-P(O)(O($C_1$-$C_6$)alkyl)$_2$, -($C_3$-$C_{10}$)cycloalkyl, ($C_6$-$C_{10}$)aryl, ($C_2$-$C_9$)heterocyclyl, -($C_1$-$C_9$)heteroaryl, -$NR^5R^6$, -$NSO_2$($C_1$-$C_6$)alkyl, -$NHSO_2$($C_3$-$C_6$)cycloalkyl, -N(($C_1$-$C_6$)alkyl)($SO_2$-$C_1$-$C_6$)alkyl), -N(($C_1$-$C_6$)alkyl)($SO_2$($C_3$-$C_6$)cycloalkyl), -O($C_1$-$C_6$)alkyl, -O-$SO_2$($C_1$-$C_6$)alkyl, -O-$SO_2$($C_1$-$C_6$)alkyl, -(CO)($C_1$-$C_6$)alkyl, -(CO)$CF_3$, -(CO)($C_3$-$C_{10}$)cycloalkyl, -(CO)($C_6$-$C_{10}$)aryl, -(CO)($C_2$-$C_9$)heterocyclyl, -(CO)($C_1$-$C_9$)heteroaryl, -(CO)O($C_1$-$C_6$)alkyl, -(CO)O($C_3$-$C_{10}$)cycloalkyl, -(CO)O($C_6$-$C_{10}$)aryl, -(CO)O($C_2$-$C_9$)heterocyclyl, -(CO)O($C_1$-$C_9$)heteroaryl, -(CO)($C_1$-$C_6$)alkyl-O($C_1$-$C_6$)alkyl, -$SO_2$($C_1$-$C_6$)alkyl, -$SO_2$($C_3$-$C_6$)cycloalkyl, $SO_2CF_3$, $SO_2NH_2$, $SO_2NH$($C_1$-$C_6$)alkyl, -$SO_2NH$($C_3$-$C_6$)cycloalkyl, -$SO_2N$(($C_1$-$C_6$)alkyl)$_2$, -$SO_2N$(($C_3$-$C_6$)cycloalkyl)$_2$, -$SO_2NR^5R^6$, and -$SO_2N$($C_1$-$C_6$)alkyl-($C_6$-$C_{10}$)aryl; wherein said -($C_3$-$C_{10}$)cycloalkyl, -($C_2$-$C_9$)heterocyclyl, and -($C_1$-$C_6$)alkyl-($C_2$-$C_9$) heterocyclyl are optionally interrupted by one to three elements selected from the group consisting of –(C=O), -$SO_2$, -S-, -O-, -N-, -NH- and –$NR^5$; and $R^5$ and $R^6$ of said $NR^5R^6$ $R^3$(b) group may be taken together with the atoms to which they are attached to form a -($C_2$-$C_9$)heterocyclyl;

(d) -($C_1$-$C_6$)alkyl optionally substituted by one to three moieties selected from the group consisting of halogen, hydroxy, -($C_1$-$C_6$)alkyl, -($C_1$-$C_6$)alkyl-P(O)(O($C_1$-$C_6$)alkyl)$_2$,

-($C_3$-$C_{10}$)cycloalkyl, ($C_6$-$C_{10}$)aryl, ($C_2$-$C_9$)heterocyclyl, -($C_1$-$C_9$)heteroaryl, -$NR^5R^6$, -$NSO_2$($C_1$-$C_6$)alkyl, -$NHSO_2$($C_3$-$C_6$)cycloalkyl, -N(($C_1$-$C_6$)alkyl)($SO_2$-$C_1$-$C_6$)alkyl), -N(($C_1$-$C_6$)alkyl)($SO_2$($C_3$-$C_6$)cycloalkyl), -O($C_1$-$C_6$)alkyl, -O-$SO_2$($C_1$-$C_6$)alkyl, -(CO)($C_1$-$C_6$)alkyl, -(CO)$CF_3$, -(CO)($C_3$-$C_{10}$)cycloalkyl, -(CO)($C_6$-$C_{10}$)aryl, -(CO)($C_2$-$C_9$)heterocyclyl, -(CO)($C_1$-$C_9$)heteroaryl, -(CO)O($C_1$-$C_6$)alkyl, -(CO)O($C_3$-$C_{10}$)cycloalkyl, -(CO)O($C_6$-$C_{10}$)aryl, -(CO)O($C_2$-$C_9$)heterocyclyl, -(CO)O($C_1$-$C_9$)heteroaryl, -(CO)($C_1$-$C_6$)alkyl-O($C_1$-$C_6$)alkyl, -$SO_2$($C_1$-$C_6$)alkyl, -$SO_2$($C_3$-$C_6$)cycloalkyl, $SO_2CF_3$, $SO_2NH_2$, $SO_2NH$($C_1$-$C_6$)alkyl, -$SO_2NH$($C_3$-$C_6$)cycloalkyl, -$SO_2N$(($C_1$-$C_6$)alkyl)$_2$, -$SO_2N$(($C_3$-$C_6$)cycloalkyl)$_2$, -$SO_2NR^5R^6$, and -$SO_2N$($C_1$-$C_6$)alkyl-($C_6$-$C_{10}$)aryl; wherein said -($C_1$-$C_6$)alkyl is optionally interrupted by one to three elements selected from the group consisting of –(C=O), -$SO_2$, -S-, -O-, -N-, -NH- and -$NR^5$; *and* $R^5$ *and* $R^6$ *of said* $NR^5R^6$ $R^3$(b) *group may be taken together with the atoms to which they are attached to form a* -($C_2$-$C_9$)heterocyclyl;

and wherein each $R^3$ (b)-(d) substituent, molety, or element is optionally substituted by one to three radicals independently selected from the group consisting of hydrogen, halogen, hydroxy, $-CF_3$, $-NO_2$, -CN, -($C_1$-$C_6$)alkyl, -($C_2$-$C_6$)alkenyl, -($C_2$-$C_6$)alkynyl, -($C_3$-$C_7$)cycloalkyl, -($C_2$-$C_9$)heterocyclyl, -($C_6$-$C_{10}$)aryl, -($C_1$-$C_9$)heteroaryl, -O($C_1$-$C_6$)alkyl, -O($C_3$-$C_7$)cycloalkyl, -O($C_2$-$C_9$)heterocyclyl, -C=N-OH, -C=N-O($C_1$-$C_6$ alkyl), -$NR^5R^6$, -$SR^7$, -$SOR^7$, -$SO_2R^7$, -$CO_2R^5$, -$CONR^5R^6$, - $SO_2NR^5R^6$, -$NHCOR^5$, -$NR^5CONR^5R^6$, and -$NR^5SO_2R^7$; with the proviso that a heteroatom of the foregoing $R^3$ *(b)-(d) substituents, moieties, elements* or radicals may not be bound to an $sp^3$ carbon atom bound to another heteroatom; and wherein $R^5$ and $R^6$ of said -$NR^5R^6$, -$CONR^5R^6$, -$SO_2NR^5R^6$, and -$NR^5CONR^5R^6$ groups may be taken together with the atoms to which they are attached to form a -($C_2$-$C_9$)heterocyclyl;

$R^4$ *is a substituent selected from the group consisting of hydrogen,* ($C_1$-$C_6$)alkyl, -($C_3$-$C_7$)cycloalkyl, and -($C_2$-$C_9$)heterocyclyl; wherein said ($C_1$-$C_6$)alkyl, -($C_3$-$C_7$)cycloalkyl, and ($C_2$-$C_9$)heterocyclyl $R^4$ substituents are optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, -($C_1$-$C_6$)alkyl, -CN, -$NR^5_2$, -$OR^5$, -($C_3$-$C_7$)cycloalkyl, -($C_2$-$C_9$)heterocyclyl, -$CO_2R^5$, and -$CONR^5R^6$; with the proviso that a heteroatom of the foregoing $R^4$ substituents may not be bound to an $sp^3$ carbon atom bound to another heteroatom; and wherein $R^5$ and $R^6$ of said -$CONR^5R^6$ group may be taken together with the atoms to which they are attached to form a -($C_3$-$C_{10}$)cycloalkyl or -($C_2$-$C_9$)heterocyclyl;

$R^5$ and $R^6$ are each substituents independently selected from the group consisting of hydrogen, -($C_1$-$C_6$)alkyl, -($C_3$-$C_7$)cycloalkyl, -($C_2$-$C_9$)heterocyclyl, -($C_6$-$C_{10}$)aryl, and -($C_1$-$C_9$)heteroaryl; wherein said -($C_1$-$C_6$)alkyl, -($C_3$-$C_7$)cycloalkyl, -($C_2$-$C_9$)heterocyclyl, -($C_6$-$C_{10}$)aryl, and -($C_1$-$C_9$)heteroaryl $R^5$ or $R^6$ substituents are optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, $-CF_3$,

-CN, -($C_1$-$C_6$)alkyl, -NH($C_1$-$C_6$)alkyl, -NH($C_3$-$C_7$)cycloalkyl, -NH($C_2$-$C_9$)heterocyclyl, -NH($C_6$-$C_{10}$)aryl, -NH($C_1$-$C_9$)heteroaryl, -N(($C_1$-$C_6$)alkyl)$_2$, -N(($C_3$-$C_7$)cycloalkyl)$_2$, -N(($C_2$-$C_9$)heterocyclyl)$_2$, -N(($C_6$-$C_{10}$)aryl)$_2$, -N(($C_1$-$C_9$)heteroaryl)$_2$, -O($C_1$-$C_6$)alkyl, -O($C_3$-$C_7$)cycloalkyl, -O($C_2$-$C_9$)heterocyclyl, -O($C_6$-$C_{10}$)aryl, -O($C_1$-$C_9$)heteroaryl, -($C_3$-$C_7$)cycloalkyl, -($C_2$-$C_9$)heterocyclyl, -$CO_2R^7$, -$CONH_2$, -$CONHR^7$, and -$CONR^7R^8$; with the proviso that a heteroatom of the foregoing $R^5$ or $R^6$ substituents or moieties may not be bound to an $sp^3$ carbon atom bound to another heteroatoms; and wherein $R^7$ and $R^8$ of said -$CONR^7R^8$ group may be taken together with the atoms to which they are attached to form a -($C_1$-$C_9$) heteroaryl;

$R^5$ and $R^6$ may be taken together with the atom(s) to which they are attached to form a cyclic group, -($C_3$-$C_{10}$)cycloalkyl or -($C_2$-$C_9$)heterocyclyl, wherein said cyclic group is optionally substituted by one to three moieties selected from the group consisting of hydrogen, halogen, hydroxy, -$CF_3$, -$NO_2$, -CN, -($C_1$-$C_6$)alkyl, -($C_2$-$C_6$)alkenyl, -($C_2$-$C_6$)alkynyl, -C=N-OH, -C=N-O(($C_1$-$C_6$)alkyl), -$NR^5R^6$, -$OR^5$, -($C_3$-$C_7$)cycloalkyl, -($C_2$-$C_9$)heterocyclyl, -$O_2R^5$, -$CONR^5R^6$, -$CONR^5R^8$, -$SR^7$, -$SOR^7$, -$SO_2R^7$, -$SO_2NR^5R^6$, -$NHCOR^5$, -$NR^5CONR^6R^8$, and -$NR^5SO_2R^7$, wherein said –($C_2$-$C_6$)alkenyl and –($C_2$-$C_6$)alkynyl moieties of said cyclic group may be optionally substituted by one to three $R^7$ groups, and said cyclic group is optionally interrupted by one to three elements selected from the group consisting of –(C=O), -$SO_2$, -S-, -O-, -N-, -NH- and –$NR^5$, with the proviso that any of the foregoing cyclic group moieties or elements may not be bound to an $sp^3$ carbon atom that is bound to another heteroatom;

$R^7$ is a substituent selected from the group consisting of –($C_1$-$C_6$)alkyl, -($C_3$-$C_7$)cycloalkyl, -($C_2$-$C_9$)heterocyclyl, -($C_6$-$C_{10}$)aryl, and -($C_1$-$C_9$) heteroaryl; wherein said -($C_1$-$C_6$)alkyl, -($C_3$-$C_7$)cycloalkyl, -($C_2$-$C_9$)heterocyclyl, -($C_6$-$C_{10}$)aryl, and -($C_1$-$C_9$) heteroaryl $R^7$ substituents are optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, -($C_1$-$C_6$)alkyl, -$NR^5_2$, and -O($C_1$-$C_6$)alkyl, with the proviso that a heteroatom of the foregoing $R^7$ substituents or moieties may not be bound to an $sp^3$ carbon atom bound to another heteroatom;

$R^8$ is a substituent selected from the group consisting of hydrogen, -($C_1$-$C_6$)alkyl, -($C_3$-$C_7$)cycloalkyl, -($C_2$-$C_9$)heterocyclyl, -($C_6$-$C_{10}$)aryl, and -($C_1$-$C_9$) heteroaryl; wherein said -($C_1$-$C_6$)alkyl, -($C_3$-$C_7$)cycloalkyl, -($C_2$-$C_9$)heterocyclyl, -($C_6$-$C_{10}$)aryl, and -($C_1$-$C_9$) heteroaryl $R^8$ radicals are optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, -($C_1$-$C_6$)alkyl, -$NH_2$, -$NHR^9$, -$NR^9_2$, $OR^9$, -($C_3$-$C_7$)cycloalkyl, -($C_2$-$C_9$)heterocyclyl, -$CO_2R^{10}$, -$CONH_2$, -$CONHR^{10}$, and -$CONR^{10}R^{11}$; with the proviso that a heteroatom of the foregoing $R^8$ substituents or moieties may not be bound to an $sp^3$ carbon atom bound to another heteroatom; and wherein $R^{10}$ and $R^{11}$ of -$CONR^{10}R^{11}$

may be taken together with the atoms to which they are attached to form a -(C2-$C_6$)heterocyclyl;

$R^9$ and $R^{10}$ are each -($C_1$-$C_6$)alkyl and may be taken together with the atoms to which they are attached to form a -($C_2$-$C_6$)heterocyclyl; and

$R^{11}$ is hydrogen or -($C_1$-$C_6$)alkyl.

The present invention also includes isotopically-labeled compounds, which are identical to those recited in Formula 1, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine and chlorine, such as $^2H$, $^3H$, $^{13}C$, $^{14}C$, $^{15}N$, $^{18}O$, $^{17}O$, $^{31}P$, $^{32}P$, $^{35}S$, $^{18}F$, and $^{36}Cl$, respectively. Compounds of the present invention, prodrugs thereof, and pharmaceutically acceptable salts of said compounds or of said prodrugs which contain the aforementioned isotopes and/or other isotopes of other atoms are within the scope of this invention. Certain isotopically-labelled compounds of the present invention, for example those into which radioactive isotopes such as $^3H$ and $^{14}C$ are incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, i.e., $^3H$, and carbon-14, i.e., $^{14}C$, isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium, i.e., $^2H$, can afford certain therapeutic advantages resulting from greater metabolic stability, for example increased *in vivo* half-life or reduced dosage requirements and, hence, may be preferred in some circumstances. Isotopically-labelled compounds of Formula 1 of this invention and prodrugs thereof can generally be prepared by carrying out the procedures disclosed in the Schemes and/or in the Examples and Preparations below, by substituting a readily available isotopically-labelled reagent for a non-isotopically-labelled reagent.

The present invention also relates to the pharmaceutically acceptable acid addition salts of compounds of the formula 1. The acids which are used to prepare the pharmaceutically acceptable acid addition salts of the aforementioned base compounds of this invention are those which form non-toxic acid addition salts, i.e., salts containing pharmacologically acceptable anions, such as the chloride, bromide, iodide, nitrate, sulfate, bisulfate, phosphate, acid phosphate, acetate, lactate, citrate, acid citrate, tartrate, bitartrate, succinate, maleate, fumarate, gluconate, saccharate, benzoate, methanesulfonate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate and pamoate [i.e., 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)]salts.

The invention also relates to base addition salts of formula 1. The chemical bases that may be used as reagents to prepare pharmaceutically acceptable base salts of those

compounds of formula 1 that are acidic in nature are those that form non-toxic base salts with such compounds. Such non-toxic base salts include, but are not limited to those derived from such pharmacologically acceptable cations such as alkali metal cations (e.g., potassium and sodium) and alkaline earth metal cations (e.g., calcium and magnesium), ammonium or water-soluble amine addition salts such as N-methylglucamine-(meglumine), and the lower alkanolammonium and other base salts of pharmaceutically acceptable organic amines.

The phrase "pharmaceutically acceptable salt(s)", as used herein, unless otherwise indicated, includes salts of acidic or basic groups which may be present in the compounds of the present invention. The compounds of the present invention that are basic in nature are capable of forming a wide variety of salts with various inorganic and organic acids. The acids that may be used to prepare pharmaceutically acceptable acid addition salts of such basic compounds of are those that form non-toxic acid addition salts, i.e., salts containing pharmacologically acceptable anions, such as the hydrochloride, hydrobromide, hydroiodide, nitrate, sulfate, bisulfate, phosphate, acid phosphate, isonicotinate, acetate, lactate, salicylate, citrate, acid citrate, tartrate, pantothenate, bitartrate, ascorbate, succinate, maleate, gentisinate, fumarate, gluconate, glucuronate, saccharate, formate, benzoate, glutamate, methanesulfonate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate and pamoate [i.e., 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)] salts. The compounds of the present invention that include a basic moiety, such as an amino group, may form pharmaceutically acceptable salts with various amino acids, in addition to the acids mentioned above.

This invention also encompasses pharmaceutical compositions containing prodrugs of compounds of the formula 1. Compounds of formula 1 having free amino, amido, hydroxy or carboxylic groups can be converted into prodrugs. Prodrugs include compounds wherein an amino acid residue, or a polypeptide chain of two or more (e.g., two, three or four) amino acid residues which are covalently joined through peptide bonds to free amino, hydroxy or carboxylic acid groups of compounds of formula 1. The amino acid residues include the 20 naturally occurring amino acids commonly designated by three letter symbols and also include, 4-hydroxyproline, hydroxylysine, demosine, isodemosine, 3-methylhistidine, norvalin, beta-alanine, gamma-aminobutyric acid, citrulline, homocysteine, homoserine, ornithine and methionine sulfone. Prodrugs also include compounds wherein carbonates, carbamates, amides and alkyl esters that are covalently bonded to the above substituents of formula 1 through the carbonyl carbon prodrug sidechain.

This invention also encompasses compounds of formula 1 containing protective groups. One skilled in the art will also appreciate that compounds of the invention can also be prepared with certain protecting groups that are useful for purification or storage and can be removed before administration to a patient. The protection and deprotection of functional

groups is described in "Protective Groups in Organic Chemistry", edited by J.W.F. McOmie, Plenum Press (1973) and "Protective Groups in Organic Synthesis", 3rd edition, T.W. Greene and P.G.M. Wuts, Wiley-Interscience (1999).

The compounds of this invention include all stereoisomers (e.g., cis and trans isomers) and all optical isomers of compounds of the formula 1 (e.g., R and S enantiomers), as well as racemic, diastereomeric and other mixtures of such isomers.

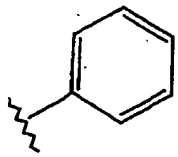
The compounds, salts and prodrugs of the present invention can exist in several tautomeric forms, including the enol and imine form, and the keto and enamine form and geometric isomers and mixtures thereof. All such tautomeric forms are included within the scope of the present invention. Tautomers exist as mixtures of a tautomeric set in solution. In solid form, usually one tautomer predominates. Even though one tautomer may be described, the present invention includes all tautomers of the present compounds.

The present invention also includes atropisomers of the present invention. Atropisomers refer to compounds of formula 1 that can be separated into rotationally restricted isomers.

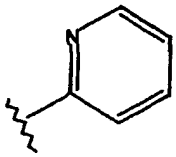
The compounds of this invention may contain olefin-like double bonds. When such bonds are present, the compounds of the invention exist as cis and trans configurations and as mixtures thereof.

A "suitable substituent" is intended to mean a chemically and pharmaceutically acceptable functional group i.e., a moiety that does not negate the biological activity of the inventive compounds. Such suitable substituents may be routinely selected by those skilled in the art. Illustrative examples of suitable substituents include, but are not limited to halo groups, perfluoroalkyl groups, perfluoroalkoxy groups, alkyl groups, alkenyl groups, alkynyl groups, hydroxy groups, oxo groups, mercapto groups, alkylthio groups, alkoxy groups, aryl or heteroaryl groups, aryloxy or heteroaryloxy groups, aralkyl or heteroaralkyl groups, aralkoxy or heteroaralkoxy groups, HO-(C=O)- groups, amino groups, alkyl- and dialkylamino groups, carbamoyl groups, alkylcarbonyl groups, alkoxycarbonyl groups, alkylaminocarbonyl groups dialkylamino carbonyl groups, arylcarbonyl groups, aryloxycarbonyl groups, alkylsulfonyl groups, arylsulfonyl groups and the like. Those skilled in the art will appreciate that many substituents can be substituted by additional substituents. Further examples of suitable substituents include those recited in the definition of compounds of Formula 1, including $R^1$ through $R^{11}$, as defined hereinabove.

The term "interrupted by" refers to compounds in which a ring carbon atom is replaced by an element selected from the group consisting of –(C=O), -$SO^2$, -S-, -O-, -N-, -NH-, and –$NR^5$. For example, if $R^7$ is –($C_6$-$C_{10}$)aryl, such as



the ring may be interrupted or replaced by a nitrogen heteroatom to form the following ring:



such that a ring carbon is replaced by the heteroatom nitrogen. Compounds of the invention can accommodate up to three such replacements or interruptions.

As used herein, the term "alkyl," as well as the alkyl moieties of other groups referred to herein (e.g., alkoxy), may be linear or branched (such as methyl, ethyl, *n*-propyl, *iso*propyl, *n*-butyl, *iso*-butyl, *secondary*-butyl, *tertiary*-butyl); optionally substituted by 1 to 3 suitable substituents as defined above such as fluoro, chloro, trifluoromethyl, ($C_1$-$C_6$)alkoxy, ($C_6$-$C_{10}$)aryloxy, trifluoromethoxy, difluoromethoxy or ($C_1$-$C_6$)alkyl. The phrase "each of said alkyl" as used herein refers to any of the preceding alkyl moieties within a group such alkoxy, alkenyl or alkylamino. Preferred alkyls include ($C_1$-$C_6$)alkyl, more preferred are ($C_1$-$C_4$)alkyl, and most preferred are methyl and ethyl.

As used herein, the term "cycloalkyl" refers to a mono, bicyclic or tricyclic carbocyclic ring (e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, cyclopentenyl, cyclohexenyl, bicyclo[2.2.1]heptanyl, bicyclo[3.2.1]octanyl and bicyclo[5.2.0]nonanyl, etc.); optionally containing 1 or 2 double bonds and optionally substituted by 1 to 3 suitable substituents as defined above such as fluoro, chloro, trifluoromethyl, ($C_1$-$C_6$)alkoxy, ($C_6$-$C_{10}$)aryloxy, trifluoromethoxy, difluoromethoxy or ($C_1$-$C_6$)alkyl.

As used herein, the term "halogen" includes fluoro, chloro, bromo or iodo or fluoride, chloride, bromide or iodide.

As used herein, the term "alkenyl" means straight or branched chain unsaturated radicals of 2 to 6 carbon atoms, including, but not limited to ethenyl, 1-propenyl, 2-propenyl (allyl), *iso*-propenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl, and the like; optionally substituted by 1 to 3 suitable substituents as defined above such as fluoro, chloro, trifluoromethyl, ($C_1$-$C_6$)alkoxy, ($C_6$-$C_{10}$)aryloxy, trifluoromethoxy, difluoromethoxy or ($C_1$-$C_6$)alkyl.

As used herein, the term "alkynyl" is used herein to mean straight or branched hydrocarbon chain radicals having one triple bond including, but not limited to, ethynyl, propynyl, butynyl, and the like; optionally substituted by 1 to 3 suitable substituents as defined

above such as fluoro, chloro, trifluoromethyl, ($C_1$-$C_6$)alkoxy, ($C_6$-$C_{10}$)aryloxy, trifluoromethoxy, difluoromethoxy or ($C_1$-$C_6$)alkyl.

As used herein, the term "carbonyl" or "(C=O)" (as used in phrases such as alkylcarbonyl, alkyl-(C=O)- or alkoxycarbonyl) refers to the joinder of the >C=O moiety to a second moiety such as an alkyl or amino group (i.e. an amido group). Alkoxycarbonylamino (i.e. alkoxy(C=O)-NH-) refers to an alkyl carbamate group. The carbonyl group is also equivalently defined herein as (C=O). Alkylcarbonylamino refers to groups such as acetamide.

As used herein, the term "aryl" means aromatic radicals such as phenyl, naphthyl, tetrahydronaphthyl, indanyl and the like; optionally substituted by 1 to 3 suitable substituents as defined above.

As used herein, the term "heteroaryl" refers to an aromatic heterocyclic group usually with one heteroatom selected from O, S and N in the ring. In addition to said heteroatom, the aromatic group may optionally have up to four N atoms in the ring. For example, heteroaryl group includes pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, thienyl, furyl, imidazolyl, pyrrolyl, oxazolyl (e.g., 1,3-oxazolyl, 1,2-oxazolyl), thiazolyl (e.g., 1,2-thiazolyl, 1,3-thiazolyl), pyrazolyl, tetrazolyl, triazolyl (e.g., 1,2,3-triazolyl, 1,2,4-triazolyl), oxadiazolyl (e.g., 1,2,3-oxadiazolyl), thiadiazolyl (e.g., 1,3,4-thiadiazolyl), quinolyl, isoquinolyl, benzothienyl, benzofuryl, indolyl, and the like; optionally substituted by 1 to 3 suitable substituents as defined above such as fluoro, chloro, trifluoromethyl, ($C_1$-$C_6$)alkoxy, ($C_6$-$C_{10}$)aryloxy, trifluoromethoxy, difluoromethoxy or ($C_1$-$C_6$)alkyl.

The term "heterocyclic" as used herein refers to a cyclic group containing 1-9 carbon atoms and 1 to 4 hetero atoms selected from N, O, $S(O)_n$ or NR. Examples of such rings include azetidinyl, tetrahydrofuranyl, imidazolidinyl, pyrrolidinyl, piperidinyl, piperazinyl, oxazolidinyl, thiazolidinyl, pyrazolidinyl, thiomorpholinyl, tetrahydrothiazinyl, tetrahydrothiadiazinyl, morpholinyl, oxetanyl, tetrahydrodiazinyl, oxazinyl, oxathiazinyl, indolinyl, isoindolinyl, quinuclidinyl, chromanyl, isochromanyl, benzoxazinyl, and the like. Examples of said monocyclic saturated or partially saturated ring systems are tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, imidazolidin-1-yl, imidazolidin-2-yl, imidazolidin-4-yl, pyrrolidin-1-yl, pyrrolidin-2-yl, pyrrolidin-3-yl, piperidin-1-yl, piperidin-2-yl, piperidin-3-yl, piperazin-1-yl, piperazin-2-yl, piperazin-3-yl, 1,3-oxazolidin-3-yl, isothiazolidine, 1,3-thiazolidin-3-yl, 1,2-pyrazolidin-2-yl, 1,3-pyrazolidin-1-yl, thiomorpholin-yl, 1,2-tetrahydrothiazin-2-yl, 1,3-tetrahydrothiazin-3-yl, tetrahydrothiadiazin-yl, morpholin-yl, 1,2-tetrahydrodiazin-2-yl, 1,3-tetrahydrodiazin-1-yl, 1,4-oxazin-2-yl, 1,2,5-oxathiazin-4-yl and the like; optionally containing 1 or 2 double bonds and optionally substituted by 1 to 3 suitable substituents as

defined above such as fluoro, chloro, trifluoromethyl, ($C_1$-$C_6$)alkoxy, ($C_6$-$C_{10}$)aryloxy, trifluoromethoxy, difluoromethoxy or ($C_1$-$C_6$)alkyl.

Nitrogen heteroatoms as used herein refers to N=, >N and -NH; wherein -N= refers to a nitrogen double bond; >N refers to a nitrogen containing two bond connections and –N refers to a nitrogen containing one bond.

"Embodiment" as used herein refers to specific groupings of compounds or uses into discrete subgenera. Such subgenera may be cognizable according to one particular substituent such as a specific $R^1$ or $R^3$ group. Other subgenera are cognizable according to combinations of various substituents, such as all compounds wherein $R^2$ is hydrogen and $R^1$ is ($C_1$-$C_6$)alkyl.

Thus, the present invention provides a compound of formula 1, wherein $R^1$ is selected from hydrogen, hydroxy, and -($C_1$-$C_6$)alkyl, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, -($C_1$-$C_6$)alkyl, -$NR^5R^6$, -$OR^5$, -($C_3$-$C_7$)cycloalkyl, -($C_2$-$C_9$)heterocyclyl, -$CO_2R^5$, -$CONR^5R^6$ and-$CONR^5R^6$.

The present invention further provides a compound of formula 1, wherein $R^1$ is -($C_1$-$C_6$)alkyl, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, -($C_1$-$C_6$)alkyl, -$NR^5R^6$, -$OR^5$, -($C_3$-$C_7$)cycloalkyl, -($C_2$-$C_9$)heterocyclyl, -$CO_2R^5$, -$CONR^5R^6$ and-$CONR^5R^6$.

The present invention also provides a compound of formula 1 wherein $R^1$ is selected from the group consisting of -($C_3$-$C_7$)cycloalkyl and -($C_2$-$C_9$)heterocyclyl, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, -($C_1$-$C_6$)alkyl, -$NR^5R^6$, -$OR^5$, -($C_3$-$C_7$)cycloalkyl, -($C_2$-$C_9$)heterocyclyl, -$CO_2R^5$, -$CONR^5R^6$ and-$CONR^5R^6$.

The invention also contemplates compounds of formula 1 wherein $R^1$ is selected from -O($C_1$-$C_6$)alkyl, -O($C_3$-$C_7$)cycloalkyl, and -O($C_2$-$C_9$)heterocyclyl, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, -($C_1$-$C_6$)alkyl, -$NR^5R^6$, -$OR^5$, -($C_3$-$C_7$)cycloalkyl, -($C_2$-$C_9$)heterocyclyl, -$CO_2R^5$, -$CONR^5R^6$ and-$CONR^5R^6$. In a preferred embodiment, $R^1$ is -O($C_1$-$C_6$)alkyl, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, -($C_1$-$C_6$)alkyl, -$NR^5R^6$, -$OR^5$, -($C_3$-$C_7$)cycloalkyl, -($C_2$-$C_9$)heterocyclyl, -$CO_2R^5$, -$CONR^5R^6$ and-$CONR^5R^6$.

One embodiment of the invention is a compound of formula 1 wherein $R^1$ is -$NR^5R^6$, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, -($C_1$-$C_6$)alkyl, -$NR^5R^6$, -$OR^5$, -($C_3$-$C_7$)cycloalkyl, -($C_2$-$C_9$)heterocyclyl, -$CO_2R^5$, -$CONR^5R^6$ and-$CONR^5R^6$.

A further embodiment of the invention is a compound of formula 1 wherein $R^1$ is selected from $-SR^7$, $-SOR^7$, $-SO_2R^7$, and $-SO_2NR^5R^6$, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, $-(C_1-C_6)$alkyl, $-NR^5R^6$, $-OR^5$, $-(C_3-C_7)$cycloalkyl, $-(C_2-C_9)$heterocyclyl, $-CO_2R^5$, $-CONR^5R^6$ and $-CONR^5R^8$. In a preferred embodiment, $R^1$ is $-SO_2NR^5R^6$, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, $-(C_1-C_6)$alkyl, $-NR^5R^6$, $-OR^5$, $-(C_3-C_7)$cycloalkyl, $-(C_2-C_9)$heterocyclyl, $-CO_2R^5$, $-CONR^5R^6$ and $-CONR^5R^8$.

The present invention also provides compounds of formula 1 wherein $R^1$ is $-CO_2R^5$, $-CONR^5R^6$, $-NHCOR^5$, $-NR^5CONR^5R^6$, or $-NR^5SO_2R^7$, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, $-(C_1-C_6)$alkyl, $-NR^5R^6$, $-OR^5$, $-(C_3-C_7)$cycloalkyl, $-(C_2-C_9)$heterocyclyl, $-CO_2R^5$, $-CONR^5R^6$ and $-CONR^5R^8$. In a preferred embodiment, $R^1$ is $-NR^5SO_2R^7$, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, $-(C_1-C_6)$alkyl, $-NR^5R^6$, $-OR^5$, $-(C_3-C_7)$cycloalkyl, $-(C_2-C_9)$heterocyclyl, $-CO_2R^5$, $-CONR^5R^6$ and $-CONR^5R^8$.

Also provided is a compound of formula 1 wherein $R^2$ is hydrogen or $-(C_1-C_6)$alkyl, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, $-NO_2$, -CN, $-(C_1-C_6)$alkyl, $-(C_2-C_6)$alkenyl, $-(C_2-C_6)$alkynyl, -C=N-OH, $-C=N-O((C_1-C_6)alkyl)$, $-NR^5R^6$, $-OR^5$, $-(C_3-C_7)$cycloalkyl, $-(C_2-C_9)$heterocyclyl, $-CO_2R^5$, $-CONR^5R^6$, $-CONR^5R^8$, $-SR^7$, $-SOR^7$, $-SO_2R^7$, $-SO_2NR^5R^6$, $-NHCOR^5$, $-NR^5CONR^5R^6$, and $-NR^5SO_2R^7$, wherein said $-(C_2-C_6)$alkenyl and $-(C_2-C_6)$alkynyl $R^2$ moieties may be optionally substituted by one to three $R^5$ groups.

Further provided is a compound of formula 1 wherein $R^2$ is $-(C_3-C_7)$cycloalkyl, or $-(C_2-C_9)$heterocyclyl, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, $-NO_2$, -CN, $-(C_1-C_6)$alkyl, $-(C_2-C_6)$alkenyl, $-(C_2-C_6)$alkynyl, -C=N-OH, $-C=N-O((C_1-C_6)alkyl)$, $-NR^5R^6$, $-OR^5$, $-(C_3-C_7)$cycloalkyl, $-(C_2-C_9)$heterocyclyl, $-CO_2R^5$, $-CONR^5R^6$, $-CONR^5R^8$, $-SR^7$, $-SOR^7$, $-SO_2R^7$, $-SO_2NR^5R^6$, $-NHCOR^5$, $-NR^5CONR^5R^6$, and $-NR^5SO_2R^7$, wherein said $-(C_2-C_6)$alkenyl and $-(C_2-C_6)$alkynyl $R^2$ moieties may be optionally substituted by one to three $R^5$ groups.

Another embodiment of the present invention is a compound of formula 1 wherein $R^2$ is $-CO_2R^5$ and $-CONR^5R^6$ optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, $-NO_2$, -CN, $-(C_1-C_6)$alkyl, $-(C_2-C_6)$alkenyl, $-(C_2-C_6)$alkynyl, -C=N-OH, $-C=N-O((C_1-C_6)alkyl)$, $-NR^5R^6$, $-OR^5$, $-(C_3-C_7)$cycloalkyl, $-(C_2-C_9)$heterocyclyl, $-CO_2R^5$, $-CONR^5R^6$, $-CONR^5R^8$, $-SR^7$, $-SOR^7$, $-SO_2R^7$,

$-SO_2NR^5R^6$, $-NHCOR^5$, $-NR^5CONR^5R^6$, and $-NR^5SO_2R^7$, wherein said $-(C_2-C_6)$alkenyl and $-(C_2-C_6)$alkynyl $R^2$ moieties may be optionally substituted by one to three $R^5$ groups.

Also provided is a compound of formula 1 wherein $R^1$ is selected from hydrogen, hydroxy, and $-(C_1-C_6)$alkyl, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, $-(C_1-C_6)$alkyl, $-NR^5R^6$, $-OR^5$, $-(C_3-C_7)$cycloalkyl, $-(C_2-C_9)$heterocyclyl, $-CO_2R^5$, $-CONR^5R^6$ and $-CONR^5R^6$; and $R^2$ is hydrogen or $-(C_1-C_6)$alkyl, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, $-NO_2$, -CN, $-(C_1-C_6)$alkyl, $-(C_2-C_6)$alkenyl, $-(C_2-C_6)$alkynyl, -C=N-OH, $-C=N-O((C_1-C_6)alkyl)$, $-NR^5R^6$, $-OR^5$, $-(C_3-C_7)$cycloalkyl, $-(C_2-C_9)$heterocyclyl, $-CO_2R^5$, $-CONR^5R^6$, $-CONR^5R^6$, $-SR^7$, $-SOR^7$, $-SO_2R^7$, $-SO_2NR^5R^6$, $-NHCOR^5$, $-NR^5CONR^5R^6$, and $-NR^5SO_2R^7$, wherein said $-(C_2-C_6)$alkenyl and $-(C_2-C_6)$alkynyl $R^2$ moieties may be optionally substituted by one to three $R^5$ groups.

The invention further provides a compound of formula 1 wherein $R^1$ is selected from hydrogen, hydroxy, and $-(C_1-C_6)$alkyl, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, $-(C_1-C_6)$alkyl, $-NR^5R^6$, $-OR^5$, $-(C_3-C_7)$cycloalkyl, $-(C_2-C_9)$heterocyclyl, $-CO_2R^5$, $-CONR^5R^6$ and $-CONR^5R^6$; and $R^2$ is hydrogen.

The present invention further provides a compound of formula 1, wherein $R^1$ is $-(C_1-C_6)$alkyl, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, $-(C_1-C_6)$alkyl, $-NR^5R^6$, $-OR^5$, $-(C_3-C_7)$cycloalkyl, $-(C_2-C_9)$heterocyclyl, $-CO_2R^5$, $-CONR^5R^6$ and $-CONR^5R^6$; and $R^2$ is hydrogen.

The present invention also provides a compound of formula 1 wherein $R^1$ is selected from the group consisting of $-(C_3-C_7)$cycloalkyl and $-(C_2-C_9)$heterocyclyl, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, $-(C_1-C_6)$alkyl, $-NR^5R^6$, $-OR^5$, $-(C_3-C_7)$cycloalkyl, $-(C_2-C_9)$heterocyclyl, $-CO_2R^5$, $-CONR^5R^6$ and $-CONR^5R^6$; and $R^2$ is hydrogen.

The invention also contemplates compounds of formula 1 wherein $R^1$ is selected from $-O(C_1-C_6)$alkyl, $-O(C_3-C_7)$cycloalkyl, and $-O(C_2-C_9)$heterocyclyl, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, $-(C_1-C_6)$alkyl, $-NR^5R^6$, $-OR^5$, $-(C_3-C_7)$cycloalkyl, $-(C_2-C_9)$heterocyclyl, $-CO_2R^5$, $-CONR^5R^6$ and $-CONR^5R^6$; and $R^2$ is hydrogen.

One embodiment of the invention is a compound of formula 1 wherein $R^1$ is $-NR^5R^6$, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, $-(C_1-C_6)$alkyl, $-NR^5R^6$, $-OR^5$,

-($C_3$-$C_7$)cycloalkyl, -($C_2$-$C_9$)heterocyclyl, -$CO_2R^5$, -$CONR^5R^6$ and-$CONR^5R^8$; and $R^2$ is hydrogen.

A further embodiment of the invention is a compound of formula 1 wherein $R^1$ is selected from -$SR^7$, -$SOR^7$, -$SO_2R^7$, and -$SO_2NR^5R^8$, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, -($C_1$-$C_6$)alkyl, -$NR^5R^6$, -$OR^5$, -($C_3$-$C_7$)cycloalkyl, -($C_2$-$C_9$)heterocyclyl, -$CO_2R^5$, -$CONR^5R^6$ and-$CONR^5R^6$; and $R^2$ is hydrogen.

The present invention also provides compounds of formula 1 wherein $R^1$ is -$CO_2R^5$, -$CONR^5R^6$, -NHCOR$^5$, -$NR^5CONR^5R^6$, or -$NR^5SO_2R^7$, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, -($C_1$-$C_6$)alkyl, -$NR^5R^6$, -$OR^5$, -($C_3$-$C_7$)cycloalkyl, -($C_2$-$C_9$)heterocyclyl, -$CO_2R^5$, -$CONR^5R^6$ and-$CONR^5R^6$; and $R^2$ is hydrogen.

Also provided is a compound of formula 1 wherein $R^2$ is hydrogen or -($C_1$-$C_6$)alkyl, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -$NO_2$, -CN, -($C_1$-$C_6$)alkyl, -($C_2$-$C_6$)alkenyl, -($C_2$-$C_6$)alkynyl, -C=N-OH, -C=N-O(($C_1$-$C_6$)alkyl), -$NR^5R^6$, -$OR^5$, -($C_3$-$C_7$)cycloalkyl, -($C_2$-$C_9$)heterocyclyl, -$CO_2R^5$, -$CONR^5R^6$, -$CONR^5R^8$, -$SR^7$, -$SOR^7$, -$SO_2R^7$, -$SO_2NR^5R^6$, -NHCOR$^5$, -$NR^5CONR^5R^6$, and -$NR^5SO_2R^7$, wherein said –($C_2$-$C_6$)alkenyl and –($C_2$-$C_6$)alkynyl $R^2$ moieties may be optionally substituted by one to three $R^5$ groups; and $R^1$ is hydrogen.

Further provided is a compound of formula 1 wherein $R^2$ is -($C_3$-$C_7$)cycloalkyl, or -($C_2$-$C_9$)heterocyclyl, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -$NO_2$, -CN, -($C_1$-$C_6$)alkyl, -($C_2$-$C_6$)alkenyl, -($C_2$-$C_6$)alkynyl, -C=N-OH, -C=N-O(($C_1$-$C_6$)alkyl), -$NR^5R^6$, -$OR^5$, -($C_3$-$C_7$)cycloalkyl, -($C_2$-$C_9$)heterocyclyl, -$CO_2R^5$, -$CONR^5R^6$, -$CONR^5R^8$, -$SR^7$, -$SOR^7$, -$SO_2R^7$, -$SO_2NR^5R^6$, -NHCOR$^5$, -$NR^5CONR^5R^6$, and -$NR^5SO_2R^7$, wherein said –($C_2$-$C_6$)alkenyl and -($C_2$-$C_6$)alkynyl $R^2$ moieties may be optionally substituted by one to three $R^5$ groups; and $R^1$ is hydrogen.

Another embodiment of the present invention is a compound of formula 1 wherein $R^2$ is -$CO_2R^5$ and -$CONR^5R^6$ optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -$NO_2$, -CN, -($C_1$-$C_6$)alkyl, -($C_2$-$C_6$)alkenyl, -($C_2$-$C_6$)alkynyl, -C=N-OH, -C=N-O(($C_1$-$C_6$)alkyl), -$NR^5R^6$, -$OR^5$, -($C_3$-$C_7$)cycloalkyl, -($C_2$-$C_9$)heterocyclyl, -$CO_2R^5$, -$CONR^5R^6$, -$CONR^5R^8$, -$SR^7$, -$SOR^7$, -$SO_2R^7$, -$SO_2NR^5R^6$, -NHCOR$^5$, -$NR^5CONR^5R^6$, and -$NR^5SO_2R^7$, wherein said –($C_2$-$C_6$)alkenyl and -($C_2$-$C_6$)alkynyl $R^2$ moieties may be optionally substituted by one to three $R^5$ groups; and $R^1$ is hydrogen.

The invention further provides a compound of formula 1 wherein $R^1$ is selected from hydrogen, hydroxy, and -($C_1$-$C_6$)alkyl, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, -($C_1$-$C_6$)alkyl, -$NR^5R^6$, -$OR^5$, -($C_3$-$C_7$)cycloalkyl, -($C_2$-$C_9$)heterocyclyl, -$CO_2R^5$, -$CONR^5R^6$ and -$CONR^5R^6$; and $R^2$ is -($C_1$-$C_6$)alkyl.

The present invention further provides a compound of formula 1, wherein $R^1$ is -($C_1$-$C_6$)alkyl, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, -($C_1$-$C_6$)alkyl, -$NR^5R^6$, -$OR^5$, -($C_3$-$C_7$)cycloalkyl, -($C_2$-$C_9$)heterocyclyl, -$CO_2R^5$, -$CONR^5R^6$ and-$CONR^5R^6$; and $R^2$ is -($C_1$-$C_6$)alkyl.

The present invention also provides a compound of formula 1 wherein $R^1$ is selected from the group consisting of -($C_3$-$C_7$)cycloalkyl and -($C_2$-$C_9$)heterocyclyl, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, -($C_1$-$C_6$)alkyl, -$NR^5R^6$, -$OR^5$, -($C_3$-$C_7$)cycloalkyl, -($C_2$-$C_9$)heterocyclyl, -$CO_2R^5$, -$CONR^5R^6$ and-$CONR^5R^6$; and $R^2$ is -($C_1$-$C_6$)alkyl.

The invention also contemplates compounds of formula 1 wherein $R^1$ is selected from -O($C_1$-$C_6$)alkyl, -O($C_3$-$C_7$)cycloalkyl, and -O($C_2$-$C_9$)heterocyclyl, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, -($C_1$-$C_6$)alkyl, -$NR^5R^6$, -$OR^5$, -($C_3$-$C_7$)cycloalkyl, -($C_2$-$C_9$)heterocyclyl, -$CO_2R^5$, -$CONR^5R^6$ and-$CONR^5R^6$; and $R^2$ is -($C_1$-$C_6$)alkyl.

One embodiment of the invention is a compound of formula 1 wherein $R^1$ is -$NR^5R^6$, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, -($C_1$-$C_6$)alkyl, -$NR^5R^6$, -$OR^5$, -($C_3$-$C_7$)cycloalkyl, -($C_2$-$C_9$)heterocyclyl, -$CO_2R^5$, -$CONR^5R^6$ and-$CONR^5R^6$; and $R^2$ is -($C_1$-$C_6$)alkyl.

A further embodiment of the invention is a compound of formula 1 wherein $R^1$ is selected from -$SR^7$, -$SOR^7$, -$SO_2R^7$, and -$SO_2NR^5R^6$, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, -($C_1$-$C_6$)alkyl, -$NR^5R^6$, -$OR^5$, -($C_3$-$C_7$)cycloalkyl, -($C_2$-$C_9$)heterocyclyl, -$CO_2R^5$, -$CONR^5R^6$ and-$CONR^5R^6$; and $R^2$ is -($C_1$-$C_6$)alkyl.

The present invention also provides compounds of formula 1 wherein $R^1$ is -$CO_2R^5$, -$CONR^5R^6$, -NHCO$R^5$, -$NR^5CONR^6R^6$, or -$NR^5SO_2R^7$, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, -($C_1$-$C_6$)alkyl, -$NR^5R^6$, -$OR^5$, -($C_3$-$C_7$)cycloalkyl, -($C_2$-$C_9$)heterocyclyl, -$CO_2R^5$, -$CONR^5R^6$ and-$CONR^5R^6$; and $R^2$ is -($C_1$-$C_6$)alkyl.

Also provided is a compound of formula 1 wherein $R^2$ is hydrogen or -($C_1$-$C_6$)alkyl, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, $-NO_2$, -CN, -($C_1$-$C_6$)alkyl, -($C_2$-$C_6$)alkenyl, -($C_2$-$C_6$)alkynyl, -C=N-OH, -C=N-O(($C_1$-$C_6$)alkyl), $-NR^5R^6$, $-OR^5$, -($C_3$-$C_7$)cycloalkyl, -($C_2$-$C_9$)heterocyclyl, $-CO_2R^5$, $-CONR^5R^6$, $-CONR^6R^8$, $-SR^7$, $-SOR^7$, $-SO_2R^7$, $-SO_2NR^5R^6$, $-NHCOR^5$, $-NR^5CONR^5R^6$, and $-NR^5SO_2R^7$, wherein said –($C_2$-$C_6$)alkenyl and –($C_2$-$C_6$)alkynyl $R^2$ moieties may be optionally substituted by one to three $R^6$ groups; and $R^1$ is -($C_1$-$C_6$)alkyl.

Further provided is a compound of formula 1 wherein $R^2$ is -($C_3$-$C_7$)cycloalkyl, or -($C_2$-$C_9$)heterocyclyl, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, $-NO_2$, -CN, -($C_1$-$C_6$)alkyl, -($C_2$-$C_6$)alkenyl, -($C_2$-$C_8$)alkynyl, -C=N-OH, -C=N-O(($C_1$-$C_6$)alkyl), $-NR^5R^6$, $-OR^5$, -($C_3$-$C_7$)cycloalkyl, -($C_2$-$C_9$)heterocyclyl, $-CO_2R^5$, $-CONR^5R^6$, $-CONR^5R^8$, $-SR^7$, $-SOR^7$, $-SO_2R^7$, $-SO_2NR^5R^6$, $-NHCOR^5$, $-NR^5CONR^5R^6$, and $-NR^5SO_2R^7$, wherein said –($C_2$-$C_6$)alkenyl and -($C_2$-$C_6$)alkynyl $R^2$ moieties may be optionally substituted by one to three $R^5$ groups; and $R^1$ is -($C_1$-$C_6$)alkyl.

Another embodiment of the present invention is a compound of formula 1 wherein $R^2$ is $-CO_2R^5$ and $-CONR^5R^6$ optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, $-NO_2$, -CN, -($C_1$-$C_6$)alkyl, -($C_2$-$C_6$)alkenyl, -($C_2$-$C_6$)alkynyl, -C=N-OH, -C=N-O(($C_1$-$C_6$)alkyl), $-NR^5R^6$, $-OR^5$, -($C_3$-$C_7$)cycloalkyl, -($C_2$-$C_9$)heterocyclyl, $-CO_2R^5$, $-CONR^5R^6$, $-CONR^5R^8$, $-SR^7$, $-SOR^7$, $-SO_2R^7$, $-SO_2NR^5R^6$, $-NHCOR^5$, $-NR^5CONR^5R^6$, and $-NR^5SO_2R^7$, wherein said –($C_2$-$C_6$)alkenyl and -($C_2$-$C_6$)alkynyl $R^2$ moieties may be optionally substituted by one to three $R^5$ groups; and $R^1$ is -($C_1$-$C_6$)alkyl.

Also provided is a compound of formula 1 wherein $R^1$ is selected from hydrogen, hydroxy, and -($C_1$-$C_6$)alkyl, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, -($C_1$-$C_6$)alkyl, $-NR^5R^6$, $-OR^6$, -($C_3$-$C_7$)cycloalkyl, -($C_2$-$C_9$)heterocyclyl, $-CO_2R^5$, $-CONR^5R^6$ and-$CONR^5R^6$; $R^2$ is hydrogen or -($C_1$-$C_6$)alkyl, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, $-NO_2$, -CN, -($C_1$-$C_6$)alkyl, -($C_2$-$C_6$)alkenyl, -($C_2$-$C_6$)alkynyl, -C=N-OH, -C=N-O(($C_1$-$C_6$)alkyl), $-NR^5R^6$, $-OR^6$, -($C_3$-$C_7$)cycloalkyl, -($C_2$-$C_9$)heterocyclyl, $-CO_2R^5$, $-CONR^5R^6$, $-CONR^5R^8$, $-SR^7$, $-SOR^7$, $-SO_2R^7$, $-SO_2NR^5R^6$, $-NHCOR^5$, $-NR^5CONR^5R^6$, and $-NR^5SO_2R^7$, wherein said –($C_2$-$C_6$)alkenyl and -($C_2$-$C_6$)alkynyl $R^2$ moieties may be optionally substituted by one to three $R^5$ groups; and n is 1.

The invention further provides a compound of formula 1 wherein $R^1$ is selected from hydrogen, hydroxy, and -($C_1$-$C_6$)alkyl, optionally substituted by one to three moieties

independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, -($C_1$-$C_6$)alkyl, -$NR^5R^6$, -$OR^5$, -($C_3$-$C_7$)cycloalkyl, -($C_2$-$C_9$)heterocyclyl, -$CO_2R^5$, -$CONR^5R^6$ and -$CONR^5R^6$; $R^2$ is -($C_1$-$C_6$)alkyl; and n is 1.

The present invention further provides a compound of formula 1, wherein $R^1$ is -($C_1$-$C_6$)alkyl, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, -($C_1$-$C_6$)alkyl, -$NR^5R^6$, -$OR^5$, -($C_3$-$C_7$)cycloalkyl, -($C_2$-$C_9$)heterocyclyl, -$CO_2R^5$, -$CONR^5R^6$ and-$CONR^5R^6$; $R^2$ is -($C_1$-$C_6$)alkyl; and n is 1.

The present invention also provides a compound of formula 1 wherein $R^1$ is selected from the group consisting of -($C_3$-$C_7$)cycloalkyl and -($C_2$-$C_9$)heterocyclyl, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, -($C_1$-$C_6$)alkyl, -$NR^5R^6$, -$OR^5$, -($C_3$-$C_7$)cycloalkyl, -($C_2$-$C_9$)heterocyclyl, -$CO_2R^5$, -$CONR^5R^6$ and-$CONR^5R^6$; $R^2$ is -($C_1$-$C_6$)alkyl; and n is 1.

The invention also contemplates compounds of formula 1 wherein $R^1$ is selected from -O($C_1$-$C_6$)alkyl, -O($C_3$-$C_7$)cycloalkyl, and -O($C_2$-$C_9$)heterocyclyl, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, -($C_1$-$C_6$)alkyl, -$NR^5R^6$, -$OR^5$, -($C_3$-$C_7$)cycloalkyl, -($C_2$-$C_9$)heterocyclyl, -$CO_2R^5$, -$CONR^5R^6$ and-$CONR^5R^6$; $R^2$ is -($C_1$-$C_6$)alkyl; and n is 1.

One embodiment of the invention is a compound of formula 1 wherein $R^1$ is -$NR^5R^6$, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, -($C_1$-$C_6$)alkyl, -$NR^5R^6$, -$OR^5$, -($C_3$-$C_7$)cycloalkyl, -($C_2$-$C_9$)heterocyclyl, -$CO_2R^5$, -$CONR^5R^6$ and-$CONR^5R^6$; $R^2$ is -($C_1$-$C_6$)alkyl; and n is 1.

A further embodiment of the invention is a compound of formula 1 wherein $R^1$ is selected from -$SR^7$, -$SOR^7$, -$SO_2R^7$, and -$SO_2NR^5R^6$, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, -($C_1$-$C_6$)alkyl, -$NR^5R^6$, -$OR^5$, -($C_3$-$C_7$)cycloalkyl, -($C_2$-$C_9$)heterocyclyl, -$CO_2R^5$, -$CONR^5R^6$ and-$CONR^5R^6$; $R^2$ is -($C_1$-$C_6$)alkyl; and n is 1.

The present invention also provides compounds of formula 1 wherein $R^1$ is -$CO_2R^5$, -$CONR^5R^6$, -NHCOR$^5$, -$NR^5CONR^5R^6$, or -$NR^5SO_2R^7$, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, -($C_1$-$C_6$)alkyl, -$NR^5R^6$, -$OR^5$, -($C_3$-$C_7$)cycloalkyl, -($C_2$-$C_9$)heterocyclyl, -$CO_2R^5$, -$CONR^5R^6$ and-$CONR^5R^6$; $R^2$ is -($C_1$-$C_6$)alkyl; and n is 1.

Also provided is a compound of formula 1 wherein $R^2$ is hydrogen or -($C_1$-$C_6$)alkyl, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -$NO_2$, -CN, -($C_1$-$C_6$)alkyl, -($C_2$-$C_6$)alkenyl,

-($C_2$-$C_6$)alkynyl, -C=N-OH, -C=N-O(($C_1$-$C_6$)alkyl), -$NR^5R^6$, -$OR^5$, -($C_3$-$C_7$)cycloalkyl, -($C_2$-$C_9$)heterocyclyl, -$CO_2R^5$, -$CONR^5R^6$, -$CONR^5R^6$, -$SR^7$, -$SOR^7$, -$SO_2R^7$, -$SO_2NR^5R^6$, -$NHCOR^5$, -$NR^5CONR^5R^6$, and -$NR^5SO_2R^7$, wherein said –($C_2$-$C_6$)alkenyl and –($C_2$-$C_6$)alkynyl $R^2$ moieties may be optionally substituted by one to three $R^5$ groups; $R^1$ is -($C_1$-$C_6$)alkyl; and n is 1.

Further provided is a compound of formula 1 wherein $R^2$ is -($C_3$-$C_7$)cycloalkyl, or -($C_2$-$C_9$)heterocyclyl, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -$NO_2$, -CN, -($C_1$-$C_6$)alkyl, -($C_2$-$C_6$)alkenyl, -($C_2$-$C_6$)alkynyl, -C=N-OH, -C=N-O(($C_1$-$C_6$)alkyl), -$NR^5R^6$, -$OR^5$, -($C_3$-$C_7$)cycloalkyl, -($C_2$-$C_9$)heterocyclyl, -$CO_2R^5$, -$CONR^5R^6$, -$CONR^5R^6$, -$SR^7$, -$SOR^7$, -$SO_2R^7$, -$SO_2NR^5R^6$, -$NHCOR^5$, -$NR^5CONR^5R^6$, and -$NR^5SO_2R^7$, wherein said –($C_2$-$C_6$)alkenyl and -($C_2$-$C_6$)alkynyl $R^2$ moieties may be optionally substituted by one to three $R^5$ groups; $R^1$ is -($C_1$-$C_6$)alkyl; and n is 1.

Another embodiment of the present invention is a compound of formula 1 wherein $R^2$ is -$CO_2R^5$ and -$CONR^5R^6$ optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -$NO_2$, -CN, -($C_1$-$C_6$)alkyl, -($C_2$-$C_6$)alkenyl, -($C_2$-$C_6$)alkynyl, -C=N-OH, -C=N-O(($C_1$-$C_6$)alkyl), -$NR^5R^6$, -$OR^5$, -($C_3$-$C_7$)cycloalkyl, -($C_2$-$C_9$)heterocyclyl, -$CO_2R^5$, -$CONR^5R^6$, -$CONR^5R^6$, -$SR^7$, -$SOR^7$, -$SO_2R^7$, -$SO_2NR^5R^6$, -$NHCOR^5$, -$NR^5CONR^5R^6$, and -$NR^5SO_2R^7$, wherein said –($C_2$-$C_6$)alkenyl and -($C_2$-$C_6$)alkynyl $R^2$ moieties may be optionally substituted by one to three $R^5$ groups; $R^1$ is -($C_1$-$C_6$)alkyl; and n is 1.

The invention further provides a compound of formula 1 wherein $R^1$ is selected from hydrogen, hydroxy, and -($C_1$-$C_6$)alkyl, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, -($C_1$-$C_6$)alkyl, -$NR^5R^6$, -$OR^5$, -($C_3$-$C_7$)cycloalkyl, -($C_2$-$C_9$)heterocyclyl, -$CO_2R^5$, -$CONR^5R^6$ and -$CONR^5R^6$; $R^2$ is -($C_1$-$C_6$)alkyl; and n is 1.

The present invention further provides a compound of formula 1, wherein $R^1$ is -($C_1$-$C_6$)alkyl, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, -($C_1$-$C_6$)alkyl, -$NR^5R^6$, -$OR^5$, -($C_3$-$C_7$)cycloalkyl, -($C_2$-$C_9$)heterocyclyl, -$CO_2R^5$, -$CONR^5R^6$ and-$CONR^5R^6$; $R^2$ is -($C_1$-$C_6$)alkyl; and n is 1.

The present invention also provides a compound of formula 1 wherein $R^1$ is selected from the group consisting of -($C_3$-$C_7$)cycloalkyl and -($C_2$-$C_9$)heterocyclyl, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, -($C_1$-$C_6$)alkyl, -$NR^5R^6$, -$OR^5$, -($C_3$-$C_7$)cycloalkyl, -($C_2$-$C_9$)heterocyclyl, -$CO_2R^5$, -$CONR^5R^6$ and-$CONR^5R^6$; $R^2$ is -($C_1$-$C_6$)alkyl; and n is 1.

The invention also contemplates compounds of formula 1 wherein $R^1$ is selected from $-O(C_1-C_6)$alkyl, $-O(C_3-C_7)$cycloalkyl, and $-O(C_2-C_9)$heterocyclyl, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, $-(C_1-C_6)$alkyl, $-NR^5R^6$, $-OR^5$, $-(C_3-C_7)$cycloalkyl, $-(C_2-C_9)$heterocyclyl, $-CO_2R^5$, $-CONR^5R^6$ and $-CONR^5R^6$; $R^2$ is $-(C_1-C_6)$alkyl; and n is 1.

One embodiment of the invention is a compound of formula 1 wherein $R^1$ is $-NR^5R^6$, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, $-(C_1-C_6)$alkyl, $-NR^5R^6$, $-OR^5$, $-(C_3-C_7)$cycloalkyl, $-(C_2-C_9)$heterocyclyl, $-CO_2R^5$, $-CONR^5R^6$ and $-CONR^5R^6$; $R^2$ is $-(C_1-C_6)$alkyl; and n is 1.

A further embodiment of the invention is a compound of formula 1 wherein $R^1$ is selected from $-SR^7$, $-SOR^7$, $-SO_2R^7$, and $-SO_2NR^5R^6$, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, $-(C_1-C_6)$alkyl, $-NR^5R^6$, $-OR^5$, $-(C_3-C_7)$cycloalkyl, $-(C_2-C_9)$heterocyclyl, $-CO_2R^5$, $-CONR^5R^6$ and $-CONR^5R^6$; $R^2$ is $-(C_1-C_6)$alkyl; and n is 1.

The present invention also provides compounds of formula 1 wherein $R^1$ is $-CO_2R^5$, $-CONR^5R^6$, $-NHCOR^5$, $-NR^5CONR^5R^6$, or $-NR^5SO_2R^7$, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, $-(C_1-C_6)$alkyl, $-NR^5R^6$, $-OR^5$, $-(C_3-C_7)$cycloalkyl, $-(C_2-C_9)$heterocyclyl, $-CO_2R^5$, $-CONR^5R^6$ and $-CONR^5R^6$; $R^2$ is $-(C_1-C_6)$alkyl; and n is 1.

Also provided is a compound of formula 1 wherein $R^2$ is hydrogen or $-(C_1-C_6)$alkyl, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, $-NO_2$, -CN, $-(C_1-C_6)$alkyl, $-(C_2-C_6)$alkenyl, $-(C_2-C_6)$alkynyl, -C=N-OH, -C=N-O($(C_1-C_6)$alkyl), $-NR^5R^6$, $-OR^5$, $-(C_3-C_7)$cycloalkyl, $-(C_2-C_9)$heterocyclyl, $-CO_2R^5$, $-CONR^5R^6$, $-CONR^5R^6$, $-SR^7$, $-SOR^7$, $-SO_2R^7$, $-SO_2NR^5R^6$, $-NHCOR^5$, $-NR^5CONR^5R^6$, and $-NR^5SO_2R^7$, wherein said $-(C_2-C_6)$alkenyl and $-(C_2-C_6)$alkynyl $R^2$ moieties may be optionally substituted by one to three $R^5$ groups; $R^1$ is $-(C_1-C_6)$alkyl; and n is 1.

Further provided is a compound of formula 1 wherein $R^2$ is $-(C_3-C_7)$cycloalkyl, or $-(C_2-C_9)$heterocyclyl, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, $-NO_2$, -CN, $-(C_1-C_6)$alkyl, $-(C_2-C_6)$alkenyl, $-(C_2-C_6)$alkynyl, -C=N-OH, -C=N-O($(C_1-C_6)$alkyl), $-NR^5R^6$, $-OR^5$, $-(C_3-C_7)$cycloalkyl, $-(C_2-C_9)$heterocyclyl, $-CO_2R^5$, $-CONR^5R^6$, $-CONR^5R^6$, $-SR^7$, $-SOR^7$, $-SO_2R^7$, $-SO_2NR^5R^6$, $-NHCOR^5$, $-NR^5CONR^5R^6$, and $-NR^5SO_2R^7$, wherein said $-(C_2-C_6)$alkenyl and $-(C_2-C_6)$alkynyl $R^2$ moieties may be optionally substituted by one to three $R^5$ groups; $R^1$ is $-(C_1-C_6)$alkyl; and n is 1.

Another embodiment of the present invention is a compound of formula 1 wherein $R^2$ is $-CO_2R^5$ and $-CONR^5R^6$ optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, $-NO_2$, -CN, $-(C_1-C_6)$alkyl, $-(C_2-C_6)$alkenyl, $-(C_2-C_6)$alkynyl, -C=N-OH, $-C=N-O((C_1-C_6)alkyl)$, $-NR^5R^6$, $-OR^5$, $-(C_3-C_7)$cycloalkyl, $-(C_2-C_9)$heterocyclyl, $-CO_2R^5$, $-CONR^5R^6$, $-CONR^5R^6$, $-SR^7$, $-SOR^7$, $-SO_2R^7$, $-SO_2NR^5R^6$, $-NHCOR^5$, $-NR^5CONR^5R^6$, and $-NR^5SO_2R^7$, wherein said $-(C_2-C_6)$alkenyl and $-(C_2-C_6)$alkynyl $R^2$ moieties may be optionally substituted by one to three $R^5$ groups; $R^1$ is $-(C_1-C_6)$alkyl; and n is 1.

Also provided is a compound of formula 1 wherein $R^1$ is selected from hydrogen, hydroxy, and $-(C_1-C_6)$alkyl, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, $-(C_1-C_6)$alkyl, $-NR^5R^6$, $-OR^5$, $-(C_3-C_7)$cycloalkyl, $-(C_2-C_9)$heterocyclyl, $-CO_2R^5$, $-CONR^5R^6$ and-$CONR^5R^6$; $R^2$ is hydrogen or $-(C_1-C_6)$alkyl, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, $-NO_2$, -CN, $-(C_1-C_6)$alkyl, $-(C_2-C_6)$alkenyl, $-(C_2-C_6)$alkynyl, -C=N-OH, $-C=N-O((C_1-C_6)alkyl)$, $-NR^5R^6$, $-OR^5$, $-(C_3-C_7)$cycloalkyl, $-(C_2-C_9)$heterocyclyl, $-CO_2R^5$, $-CONR^5R^6$, $-CONR^5R^6$, $-SR^7$, $-SOR^7$, $-SO_2R^7$, $-SO_2NR^5R^6$, $-NHCOR^5$, $-NR^5CONR^5R^6$, and $-NR^5SO_2R^7$, wherein said $-(C_2-C_6)$alkenyl and $-(C_2-C_6)$alkynyl $R^2$ moieties may be optionally substituted by one to three $R^5$ groups; and n is 1.

The invention further provides a compound of formula 1 wherein $R^1$ is selected from hydrogen, hydroxy, and $-(C_1-C_6)$alkyl, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, $-(C_1-C_6)$alkyl, $-NR^5R^6$, $-OR^5$, $-(C_3-C_7)$cycloalkyl, $-(C_2-C_9)$heterocyclyl, $-CO_2R^5$, $-CONR^5R^6$ and $-CONR^5R^6$; $R^2$ is hydrogen; and n is 1.

The present invention further provides a compound of formula 1, wherein $R^1$ is $-(C_1-C_6)$alkyl, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, $-(C_1-C_6)$alkyl, $-NR^5R^6$, $-OR^5$, $-(C_3-C_7)$cycloalkyl, $-(C_2-C_9)$heterocyclyl, $-CO_2R^5$, $-CONR^5R^6$ and-$CONR^5R^6$; $R^2$ is hydrogen; and n is 1.

The present invention also provides a compound of formula 1 wherein $R^1$ is selected from the group consisting of $-(C_3-C_7)$cycloalkyl and $-(C_2-C_9)$heterocyclyl, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, $-(C_1-C_6)$alkyl, $-NR^5R^6$, $-OR^5$, $-(C_3-C_7)$cycloalkyl, $-(C_2-C_9)$heterocyclyl, $-CO_2R^5$, $-CONR^5R^6$ and-$CONR^5R^6$; $R^2$ is hydrogen; and n is 1.

The invention also contemplates compounds of formula 1 wherein $R^1$ is selected from $-O(C_1-C_6)$alkyl, $-O(C_3-C_7)$cycloalkyl, and $-O(C_2-C_6)$heterocyclyl, optionally substituted by one

to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, -($C_1$-$C_6$)alkyl, -$NR^5R^6$, -$OR^5$, -($C_3$-$C_7$)cycloalkyl, -($C_2$-$C_9$)heterocyclyl, -$CO_2R^5$, -$CONR^5R^6$ and-$CONR^5R^6$; $R^2$ is hydrogen; and n is 1.

One embodiment of the invention is a compound of formula 1 wherein $R^1$ is -$NR^5R^6$, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, -($C_1$-$C_6$)alkyl, -$NR^5R^6$, -$OR^5$, -($C_3$-$C_7$)cycloalkyl, -($C_2$-$C_9$)heterocyclyl, -$CO_2R^5$, -$CONR^5R^6$ and-$CONR^5R^6$; $R^2$ is hydrogen; and n is 1.

A further embodiment of the invention is a compound of formula 1 wherein $R^1$ is selected from -$SR^7$, -$SOR^7$, -$SO_2R^7$, and -$SO_2NR^5R^6$, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, -($C_1$-$C_6$)alkyl, -$NR^5R^6$, -$OR^5$, -($C_3$-$C_7$)cycloalkyl, -($C_2$-$C_9$)heterocyclyl, -$CO_2R^5$, -$CONR^5R^6$ and-$CONR^5R^6$; $R^2$ is hydrogen; and n is 1.

The present invention also provides compounds of formula 1 wherein $R^1$ is -$CO_2R^5$, -$CONR^5R^6$, -NHCOR$^5$, -$NR^5CONR^5R^6$, or -$NR^5SO_2R^7$, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, -($C_1$-$C_6$)alkyl, -$NR^5R^6$, -$OR^5$, -($C_3$-$C_7$)cycloalkyl, -($C_2$-$C_9$)heterocyclyl, -$CO_2R^5$, -$CONR^5R^6$ and-$CONR^5R^6$; $R^2$ is hydrogen; and n is 1.

Also provided is a compound of formula 1 wherein $R^2$ is hydrogen or -($C_1$-$C_6$)alkyl, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -$NO_2$, -CN, -($C_1$-$C_6$)alkyl, -($C_2$-$C_6$)alkenyl, -($C_2$-$C_6$)alkynyl, -C=N-OH, -C=N-O(($C_1$-$C_6$)alkyl), -$NR^5R^6$, -$OR^5$, -($C_3$-$C_7$)cycloalkyl, -($C_2$-$C_9$)heterocyclyl, -$CO_2R^5$, -$CONR^5R^6$, -$CONR^5R^6$, -$SR^7$, -$SOR^7$, -$SO_2R^7$, -$SO_2NR^5R^6$, -NHCOR$^5$, -$NR^5CONR^5R^6$, and -$NR^5SO_2R^7$, wherein said –($C_2$-$C_6$)alkenyl and –($C_2$-$C_6$)alkynyl $R^2$ moieties may be optionally substituted by one to three $R^5$ groups; $R^1$ is hydrogen; and n is 1.

Further provided is a compound of formula 1 wherein $R^2$ is -($C_3$-$C_7$)cycloalkyl, or -($C_2$-$C_9$)heterocyclyl, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -$NO_2$, -CN, -($C_1$-$C_6$)alkyl, -($C_2$-$C_6$)alkenyl, -($C_2$-$C_6$)alkynyl, -C=N-OH, -C=N-O(($C_1$-$C_6$)alkyl), -$NR^5R^6$, -$OR^5$, -($C_3$-$C_7$)cycloalkyl, -($C_2$-$C_9$)heterocyclyl, -$CO_2R^5$, -$CONR^5R^6$, -$CONR^5R^6$, -$SR^7$, -$SOR^7$, -$SO_2R^7$, -$SO_2NR^5R^6$, -NHCOR$^5$, -$NR^5CONR^5R^6$, and -$NR^5SO_2R^7$, wherein said –($C_2$-$C_6$)alkenyl and -($C_2$-$C_6$)alkynyl $R^2$ moieties may be optionally substituted by one to three $R^5$ groups; $R^1$ is hydrogen; and n is 1.

Another embodiment of the present invention is a compound of formula 1 wherein $R^2$ is -$CO_2R^5$ and -$CONR^5R^6$ optionally substituted by one to three moieties independently

selected from the group consisting of hydrogen, halogen, hydroxy, $-NO_2$, -CN, $-(C_1-C_6)$alkyl, $-(C_2-C_6)$alkenyl, $-(C_2-C_6)$alkynyl, -C=N-OH, $-C=N-O((C_1-C_6)alkyl)$, $-NR^5R^6$, $-OR^5$, $-(C_3-C_7)$cycloalkyl, $-(C_2-C_9)$heterocyclyl, $-CO_2R^5$, $-CONR^5R^6$, $-CONR^5R^8$, $-SR^7$, $-SOR^7$, $-SO_2R^7$, $-SO_2NR^5R^6$, $-NHCOR^5$, $-NR^5CONR^5R^6$, and $-NR^5SO_2R^7$, wherein said $-(C_2-C_6)$alkenyl and $-(C_2-C_6)$alkynyl $R^2$ moieties may be optionally substituted by one to three $R^6$ groups; $R^1$ is hydrogen; and n is 1.

Also provided is a compound of formula 1 wherein $R^1$ is selected from hydrogen, hydroxy, and $-(C_1-C_6)$alkyl, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, $-(C_1-C_6)$alkyl, $-NR^5R^6$, $-OR^5$, $-(C_3-C_7)$cycloalkyl, $-(C_2-C_9)$heterocyclyl, $-CO_2R^5$, $-CONR^5R^6$ and-$CONR^5R^8$; $R^2$ is hydrogen or $-(C_1-C_6)$alkyl, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, $-NO_2$, -CN, $-(C_1-C_6)$alkyl, $-(C_2-C_6)$alkenyl, $-(C_2-C_6)$alkynyl, -C=N-OH, $-C=N-O((C_1-C_6)alkyl)$, $-NR^5R^6$, $-OR^5$, $-(C_3-C_7)$cycloalkyl, $-(C_2-C_9)$heterocyclyl, $-CO_2R^5$, $-CONR^5R^6$, $-CONR^5R^8$, $-SR^7$, $-SOR^7$, $-SO_2R^7$, $-SO_2NR^5R^6$, $-NHCOR^5$, $-NR^5CONR^5R^6$, and $-NR^5SO_2R^7$, wherein said $-(C_2-C_6)$alkenyl and $-(C_2-C_6)$alkynyl $R^2$ moieties may be optionally substituted by one to three $R^5$ groups; and n is 2.

The invention further provides a compound of formula 1 wherein $R^1$ is selected from hydrogen, hydroxy, and $-(C_1-C_6)$alkyl, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, $-(C_1-C_6)$alkyl, $-NR^5R^6$, $-OR^5$, $-(C_3-C_7)$cycloalkyl, $-(C_2-C_9)$heterocyclyl, $-CO_2R^5$, $-CONR^5R^6$ and-$CONR^5R^8$; $R^2$ is $-(C_1-C_6)$alkyl; and n is 2.

The present invention further provides a compound of formula 1, wherein $R^1$ is $-(C_1-C_6)$alkyl, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, $-(C_1-C_6)$alkyl, $-NR^5R^6$, $-OR^5$, $-(C_3-C_7)$cycloalkyl, $-(C_2-C_9)$heterocyclyl, $-CO_2R^5$, $-CONR^5R^6$ and-$CONR^5R^8$; $R^2$ is $-(C_1-C_6)$alkyl; and n is 2.

The present invention also provides a compound of formula 1 wherein $R^1$ is selected from the group consisting of $-(C_3-C_7)$cycloalkyl and $-(C_2-C_9)$heterocyclyl, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, $-(C_1-C_6)$alkyl, $-NR^5R^6$, $-OR^5$, $-(C_3-C_7)$cycloalkyl, $-(C_2-C_9)$heterocyclyl, $-CO_2R^5$, $-CONR^5R^6$ and-$CONR^5R^8$; $R^2$ is $-(C_1-C_6)$alkyl; and n is 2.

The invention also contemplates compounds of formula 1 wherein $R^1$ is selected from $-O(C_1-C_6)$alkyl, $-O(C_3-C_7)$cycloalkyl, and $-O(C_2-C_9)$heterocyclyl, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen,

hydroxy, -CN, -($C_1$-$C_6$)alkyl, -$NR^5R^6$, -$OR^5$, -($C_3$-$C_7$)cycloalkyl, -($C_2$-$C_9$)heterocyclyl, -$CO_2R^5$, -$CONR^5R^6$ and-$CONR^5R^8$; $R^2$ is -($C_1$-$C_6$)alkyl; and n is 2.

One embodiment of the invention is a compound of formula 1 wherein $R^1$ is -$NR^5R^6$, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, -($C_1$-$C_6$)alkyl, -$NR^5R^6$, -$OR^5$, -($C_3$-$C_7$)cycloalkyl, -($C_2$-$C_9$)heterocyclyl, -$CO_2R^5$, -$CONR^5R^6$ and-$CONR^5R^8$; $R^2$ is -($C_1$-$C_6$)alkyl; and n is 2.

A further embodiment of the invention is a compound of formula 1 wherein $R^1$ is selected from -$SR^7$, -$SOR^7$, -$SO_2R^7$, and -$SO_2NR^5R^6$, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, -($C_1$-$C_6$)alkyl, -$NR^5R^6$, -$OR^5$, -($C_3$-$C_7$)cycloalkyl, -($C_2$-$C_9$)heterocyclyl, -$CO_2R^5$, -$CONR^5R^6$ and-$CONR^5R^8$; $R^2$ is -($C_1$-$C_6$)alkyl; and n is 2.

The present invention also provides compounds of formula 1 wherein $R^1$ is -$CO_2R^5$, -$CONR^5R^6$, -NHCOR$^5$, -$NR^5CONR^5R^6$, or -$NR^5SO_2R^7$, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, -($C_1$-$C_6$)alkyl, -$NR^5R^6$, -$OR^5$, -($C_3$-$C_7$)cycloalkyl, -($C_2$-$C_9$)heterocyclyl, -$CO_2R^5$, -$CONR^5R^6$ and-$CONR^5R^8$; $R^2$ is -($C_1$-$C_6$)alkyl; and n is 2.

Also provided is a compound of formula 1 wherein $R^2$ is hydrogen or -($C_1$-$C_6$)alkyl, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -$NO_2$, -CN, -($C_1$-$C_6$)alkyl, -($C_2$-$C_6$)alkenyl, -($C_2$-$C_6$)alkynyl, -C=N-OH, -C=N-O(($C_1$-$C_6$)alkyl), -$NR^5R^6$, -$OR^5$, -($C_3$-$C_7$)cycloalkyl, -($C_2$-$C_9$)heterocyclyl, -$CO_2R^5$, -$CONR^5R^6$, -$CONR^5R^6$, -$SR^7$, -$SOR^7$, -$SO_2R^7$, -$SO_2NR^5R^6$, -NHCOR$^5$, -$NR^5CONR^5R^6$, and -$NR^5SO_2R^7$, wherein said –($C_2$-$C_6$)alkenyl and –($C_2$-$C_6$)alkynyl $R^2$ moieties may be optionally substituted by one to three $R^5$ groups; $R^1$ is -($C_1$-$C_6$)alkyl; and n is 2.

Further provided is a compound of formula 1 wherein $R^2$ is -($C_3$-$C_7$)cycloalkyl, or -($C_2$-$C_9$)heterocyclyl, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -$NO_2$, -CN, -($C_1$-$C_6$)alkyl, -($C_2$-$C_6$)alkenyl, -($C_2$-$C_6$)alkynyl, -C=N-OH, -C=N-O(($C_1$-$C_6$)alkyl), -$NR^5R^6$, -$OR^5$, -($C_3$-$C_7$)cycloalkyl, -($C_2$-$C_9$)heterocyclyl, -$CO_2R^5$, -$CONR^5R^6$, -$CONR^5R^8$, -$SR^7$, -$SOR^7$, -$SO_2R^7$, -$SO_2NR^5R^6$, -NHCOR$^5$, -$NR^5CONR^5R^6$, and -$NR^5SO_2R^7$, wherein said –($C_2$-$C_6$)alkenyl and -($C_2$-$C_6$)alkynyl $R^2$ moieties may be optionally substituted by one to three $R^5$ groups; $R^1$ is -($C_1$-$C_6$)alkyl; and n is 2.

Another embodiment of the present invention is a compound of formula 1 wherein $R^2$ is -$CO_2R^5$ and -$CONR^5R^6$ optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -$NO_2$, -CN, -($C_1$-$C_6$)alkyl,

-($C_2$-$C_6$)alkenyl, -($C_2$-$C_6$)alkynyl, -C=N-OH, -C=N-O(($C_1$-$C_6$)alkyl), -$NR^5R^6$, -$OR^5$, -($C_3$-$C_7$)cycloalkyl, -($C_2$-$C_9$)heterocyclyl, -$CO_2R^5$, -$CONR^5R^6$, -$CONR^5R^6$, -$SR^7$, -$SOR^7$, -$SO_2R^7$, -$SO_2NR^5R^6$, -$NHCOR^5$, -$NR^5CONR^5R^6$, and -$NR^5SO_2R^7$, wherein said -($C_2$-$C_6$)alkenyl and -($C_2$-$C_6$)alkynyl $R^2$ moieties may be optionally substituted by one to three $R^5$ groups; $R^1$ is -($C_1$-$C_6$)alkyl; and n is 2.

The invention further provides a compound of formula 1 wherein $R^1$ is selected from hydrogen, hydroxy, and -($C_1$-$C_6$)alkyl, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, -($C_1$-$C_6$)alkyl, -$NR^5R^6$, -$OR^5$, -($C_3$-$C_7$)cycloalkyl, -($C_2$-$C_9$)heterocyclyl, -$CO_2R^5$, -$CONR^5R^6$ and -$CONR^5R^8$; $R^2$ is -($C_1$-$C_6$)alkyl; and n is 2.

The present invention further provides a compound of formula 1, wherein $R^1$ is -($C_1$-$C_6$)alkyl, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, -($C_1$-$C_6$)alkyl, -$NR^5R^6$, -$OR^5$, -($C_3$-$C_7$)cycloalkyl, -($C_2$-$C_9$)heterocyclyl, -$CO_2R^5$, -$CONR^5R^6$ and-$CONR^5R^8$; $R^2$ is -($C_1$-$C_6$)alkyl; and n is 2.

The present invention also provides a compound of formula 1 wherein $R^1$ is selected from the group consisting of -($C_3$-$C_7$)cycloalkyl and -($C_2$-$C_9$)heterocyclyl, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, -($C_1$-$C_6$)alkyl, -$NR^5R^6$, -$OR^5$, -($C_3$-$C_7$)cycloalkyl, -($C_2$-$C_9$)heterocyclyl, -$CO_2R^5$, -$CONR^5R^6$ and-$CONR^5R^8$; $R^2$ is -($C_1$-$C_6$)alkyl; and n is 2.

The invention also contemplates compounds of formula 1 wherein $R^1$ is selected from -O($C_1$-$C_6$)alkyl, -O($C_3$-$C_7$)cycloalkyl, and -O($C_2$-$C_9$)heterocyclyl, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, -($C_1$-$C_6$)alkyl, -$NR^5R^6$, -$OR^5$, -($C_3$-$C_7$)cycloalkyl, -($C_2$-$C_9$)heterocyclyl, -$CO_2R^5$, -$CONR^5R^6$ and-$CONR^5R^8$; $R^2$ is -($C_1$-$C_6$)alkyl; and n is 2.

One embodiment of the invention is a compound of formula 1 wherein $R^1$ is -$NR^5R^6$, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, -($C_1$-$C_6$)alkyl, -$NR^5R^6$, -$OR^5$, -($C_3$-$C_7$)cycloalkyl, -($C_2$-$C_9$)heterocyclyl, -$CO_2R^5$, -$CONR^5R^6$ and-$CONR^5R^8$; $R^2$ is -($C_1$-$C_6$)alkyl; and n is 2.

A further embodiment of the invention is a compound of formula 1 wherein $R^1$ is selected from -$SR^7$, -$SOR^7$, -$SO_2R^7$, and -$SO_2NR^5R^6$, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, -($C_1$-$C_6$)alkyl, -$NR^5R^6$, -$OR^5$, -($C_3$-$C_7$)cycloalkyl, -($C_2$-$C_9$)heterocyclyl, -$CO_2R^5$, -$CONR^5R^6$ and-$CONR^5R^8$; $R^2$ is -($C_1$-$C_6$)alkyl; and n is 2.

The present invention also provides compounds of formula 1 wherein $R^1$ is $-CO_2R^5$, $-CONR^5R^6$, $-NHCOR^6$, $-NR^5CONR^5R^6$, or $-NR^5SO_2R^7$, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, $-(C_1-C_6)$alkyl, $-NR^5R^6$, $-OR^5$, $-(C_3-C_7)$cycloalkyl, $-(C_2-C_9)$heterocyclyl, $-CO_2R^5$, $-CONR^5R^6$ and $-CONR^5R^6$; $R^2$ is $-(C_1-C_6)$alkyl; and n is 2.

Also provided is a compound of formula 1 wherein $R^2$ is hydrogen or $-(C_1-C_6)$alkyl, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, $-NO_2$, -CN, $-(C_1-C_6)$alkyl, $-(C_2-C_6)$alkenyl, $-(C_2-C_6)$alkynyl, -C=N-OH, $-C=N-O((C_1-C_6)alkyl)$, $-NR^5R^6$, $-OR^5$, $-(C_3-C_7)$cycloalkyl, $-(C_2-C_9)$heterocyclyl, $-CO_2R^5$, $-CONR^5R^6$, $-CONR^5R^6$, $-SR^7$, $-SOR^7$, $-SO_2R^7$, $-SO_2NR^5R^6$, $-NHCOR^5$, $-NR^5CONR^5R^6$, and $-NR^5SO_2R^7$, wherein said $-(C_2-C_6)$alkenyl and $-(C_2-C_6)$alkynyl $R^2$ moieties may be optionally substituted by one to three $R^5$ groups; $R^1$ is $-(C_1-C_6)$alkyl; and n is 2.

Further provided is a compound of formula 1 wherein $R^2$ is $-(C_3-C_7)$cycloalkyl, or $-(C_2-C_9)$heterocyclyl, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, $-NO_2$, -CN, $-(C_1-C_6)$alkyl, $-(C_2-C_6)$alkenyl, $-(C_2-C_6)$alkynyl, -C=N-OH, $-C=N-O((C_1-C_6)alkyl)$, $-NR^5R^6$, $-OR^5$, $-(C_3-C_7)$cycloalkyl, $-(C_2-C_9)$heterocyclyl, $-CO_2R^5$, $-CONR^5R^6$, $-CONR^5R^6$, $-SR^7$, $-SOR^7$, $-SO_2R^7$, $-SO_2NR^5R^6$, $-NHCOR^5$, $-NR^5CONR^5R^6$, and $-NR^5SO_2R^7$, wherein said $-(C_2-C_6)$alkenyl and $-(C_2-C_6)$alkynyl $R^2$ moieties may be optionally substituted by one to three $R^5$ groups; $R^1$ is $-(C_1-C_6)$alkyl; and n is 2.

Another embodiment of the present invention is a compound of formula 1 wherein $R^2$ is $-CO_2R^5$ and $-CONR^5R^6$ optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, $-NO_2$, -CN, $-(C_1-C_6)$alkyl, $-(C_2-C_6)$alkenyl, $-(C_2-C_6)$alkynyl, -C=N-OH, $-C=N-O((C_1-C_6)alkyl)$, $-NR^5R^6$, $-OR^5$, $-(C_3-C_7)$cycloalkyl, $-(C_2-C_9)$heterocyclyl, $-CO_2R^5$, $-CONR^5R^6$, $-CONR^5R^6$, $-SR^7$, $-SOR^7$, $-SO_2R^7$, $-SO_2NR^5R^6$, $-NHCOR^5$, $-NR^5CONR^5R^6$, and $-NR^5SO_2R^7$, wherein said $-(C_2-C_6)$alkenyl and $-(C_2-C_6)$alkynyl $R^2$ moieties may be optionally substituted by one to three $R^5$ groups; $R^1$ is $-(C_1-C_6)$alkyl; and n is 2.

Also provided is a compound of formula 1 wherein $R^1$ is selected from hydrogen, hydroxy, and $-(C_1-C_6)$alkyl, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, $-(C_1-C_6)$alkyl, $-NR^5R^6$, $-OR^5$, $-(C_3-C_7)$cycloalkyl, $-(C_2-C_9)$heterocyclyl, $-CO_2R^5$, $-CONR^5R^6$ and $-CONR^5R^6$; $R^2$ is hydrogen or $-(C_1-C_6)$alkyl, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, $-NO_2$, -CN, $-(C_1-C_6)$alkyl, $-(C_2-C_6)$alkenyl, $-(C_2-C_6)$alkynyl, -C=N-OH, $-C=N-O((C_1-C_6)alkyl)$, $-NR^5R^6$, $-OR^5$,

-($C_3$-$C_7$)cycloalkyl, -($C_2$-$C_9$)heterocyclyl, -$CO_2R^5$, -$CONR^5R^6$, -$CONR^5R^8$, -$SR^7$, -$SOR^7$, -$SO_2R^7$, -$SO_2NR^5R^6$, -$NHCOR^5$, -$NR^5CONR^5R^6$, and -$NR^5SO_2R^7$, wherein said -($C_2$-$C_8$)alkenyl and -($C_2$-$C_8$)alkynyl $R^2$ moieties may be optionally substituted by one to three $R^5$ groups; and n is 2.

The invention further provides a compound of formula 1 wherein $R^1$ is selected from hydrogen, hydroxy, and -($C_1$-$C_8$)alkyl, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, -($C_1$-$C_8$)alkyl, -$NR^5R^6$, -$OR^5$, -($C_3$-$C_7$)cycloalkyl, -($C_2$-$C_9$)heterocyclyl, -$CO_2R^5$, -$CONR^5R^6$ and -$CONR^5R^8$; $R^2$ is hydrogen; and n is 2.

The present invention further provides a compound of formula 1, wherein $R^1$ is -($C_1$-$C_8$)alkyl, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, -($C_1$-$C_8$)alkyl, -$NR^5R^6$, -$OR^5$, -($C_3$-$C_7$)cycloalkyl, -($C_2$-$C_9$)heterocyclyl, -$CO_2R^5$, -$CONR^5R^6$ and-$CONR^5R^8$; $R^2$ is hydrogen; and n is 2.

The present invention also provides a compound of formula 1 wherein $R^1$ is selected from the group consisting of -($C_3$-$C_7$)cycloalkyl and -($C_2$-$C_9$)heterocyclyl, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, -($C_1$-$C_8$)alkyl, -$NR^5R^6$, -$OR^5$, -($C_3$-$C_7$)cycloalkyl, -($C_2$-$C_9$)heterocyclyl, -$CO_2R^5$, -$CONR^5R^6$ and-$CONR^5R^8$; $R^2$ is hydrogen; and n is 2.

The invention also contemplates compounds of formula 1 wherein $R^1$ is selected from -O($C_1$-$C_8$)alkyl, -O($C_3$-$C_7$)cycloalkyl, and -O($C_2$-$C_9$)heterocyclyl, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, -($C_1$-$C_8$)alkyl, -$NR^5R^6$, -$OR^5$, -($C_3$-$C_7$)cycloalkyl, -($C_2$-$C_9$)heterocyclyl, -$CO_2R^5$, -$CONR^5R^6$ and-$CONR^5R^8$; $R^2$ is hydrogen; and n is 2.

One embodiment of the invention is a compound of formula 1 wherein $R^1$ is -$NR^5R^6$, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, -($C_1$-$C_8$)alkyl, -$NR^5R^6$, -$OR^5$, -($C_3$-$C_7$)cycloalkyl, -($C_2$-$C_9$)heterocyclyl, -$CO_2R^5$, -$CONR^5R^6$ and-$CONR^5R^8$; $R^2$ is hydrogen; and n is 2.

A further embodiment of the invention is a compound of formula 1 wherein $R^1$ is selected from -$SR^7$, -$SOR^7$, -$SO_2R^7$, and -$SO_2NR^5R^6$, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, -($C_1$-$C_8$)alkyl, -$NR^5R^6$, -$OR^5$, -($C_3$-$C_7$)cycloalkyl, -($C_2$-$C_9$)heterocyclyl, -$CO_2R^5$, -$CONR^5R^6$ and-$CONR^5R^8$; $R^2$ is hydrogen; and n is 2.

The present invention also provides compounds of formula 1 wherein $R^1$ is -$CO_2R^5$, -$CONR^5R^6$, -$NHCOR^5$, -$NR^5CONR^5R^6$, or -$NR^5SO_2R^7$, optionally substituted by one to three

moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, -($C_1$-$C_6$)alkyl, -$NR^5R^6$, -$OR^5$, -($C_3$-$C_7$)cycloalkyl, -($C_2$-$C_9$)heterocyclyl, -$CO_2R^5$, -$CONR^5R^6$ and-$CONR^5R^8$; $R^2$ is hydrogen; and n is 2.

Also provided is a compound of formula 1 wherein $R^2$ is hydrogen or -($C_1$-$C_6$)alkyl, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -$NO_2$, -CN, -($C_1$-$C_6$)alkyl, -($C_2$-$C_6$)alkenyl, -($C_2$-$C_6$)alkynyl, -C=N-OH, -C=N-O(($C_1$-$C_6$)alkyl), -$NR^5R^6$, -$OR^5$, -($C_3$-$C_7$)cycloalkyl, -($C_2$-$C_9$)heterocyclyl, -$CO_2R^5$, -$CONR^5R^6$, -$CONR^5R^8$, -$SR^7$, -$SOR^7$, -$SO_2R^7$, -$SO_2NR^5R^6$, -$NHCOR^5$, -$NR^5CONR^5R^6$, and -$NR^5SO_2R^7$, wherein said –($C_2$-$C_6$)alkenyl and –($C_2$-$C_6$)alkynyl $R^2$ moieties may be optionally substituted by one to three $R^5$ groups; $R^1$ is hydrogen; and n is 2.

Further provided is a compound of formula 1 wherein $R^2$ is -($C_3$-$C_7$)cycloalkyl, or -($C_2$-$C_9$)heterocyclyl, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -$NO_2$, -CN, -($C_1$-$C_6$)alkyl, -($C_2$-$C_6$)alkenyl, -($C_2$-$C_6$)alkynyl, -C=N-OH, -C=N-O(($C_1$-$C_6$)alkyl), -$NR^5R^6$, -$OR^5$, -($C_3$-$C_7$)cycloalkyl, -($C_2$-$C_9$)heterocyclyl, -$CO_2R^5$, -$CONR^5R^6$, -$CONR^5R^8$, -$SR^7$, -$SOR^7$, -$SO_2R^7$, -$SO_2NR^5R^6$, -$NHCOR^5$, -$NR^5CONR^5R^6$, and -$NR^5SO_2R^7$, wherein said –($C_2$-$C_6$)alkenyl and -($C_2$-$C_6$)alkynyl $R^2$ moieties may be optionally substituted by one to three $R^5$ groups; $R^1$ is hydrogen; and n is 2.

Another embodiment of the present invention is a compound of formula 1 wherein $R^2$ is -$CO_2R^5$ and -$CONR^5R^6$ optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -$NO_2$, -CN, -($C_1$-$C_6$)alkyl, -($C_2$-$C_6$)alkenyl, -($C_2$-$C_6$)alkynyl, -C=N-OH, -C=N-O(($C_1$-$C_6$)alkyl), -$NR^5R^6$, -$OR^5$, -($C_3$-$C_7$)cycloalkyl, -($C_2$-$C_9$)heterocyclyl, -$CO_2R^5$, -$CONR^5R^6$, -$CONR^5R^8$, -$SR^7$, -$SOR^7$, -$SO_2R^7$, -$SO_2NR^5R^6$, -$NHCOR^5$, -$NR^5CONR^5R^6$, and -$NR^5SO_2R^7$, wherein said –($C_2$-$C_6$)alkenyl and -($C_2$-$C_6$)alkynyl $R^2$ moieties may be optionally substituted by one to three $R^5$ groups; $R^1$ is hydrogen; and n is 2.

The present invention also provides a compound of formula 1 in which $R^1$ and $R^2$ are taken together with the atom(s) to which they are attached to form a -($C_3$-$C_{10}$)cycloalkyl optionally substituted by one to three moieties selected from the group consisting of a hydrogen, halogen, hydroxy, -$NO_2$, -CN, -($C_1$-$C_6$)alkyl, -($C_2$-$C_6$)alkenyl, -($C_2$-$C_6$)alkynyl, -C=N-OH, -C=N-O($C_1$-$C_6$ alkyl), -$NR^5R^6$, -$OR^5$, -($C_3$-$C_7$)cycloalkyl, -($C_2$-$C_9$)heterocyclyl, -$CO_2R^5$, -$CONR^5R^6$, -$CONR^5R^8$, -$SR^7$, -$SOR^7$, -$SO_2R^7$, -$SO_2NR^5R^6$, -$NHCOR^5$, -$NR^5CONR^5R^6$, and -$NR^5SO_2R^7$, wherein said –($C_2$-$C_6$)alkenyl and –($C_2$-$C_6$)alkynyl moieties of said cyclic group may be optionally substituted by one to three $R^5$ groups.

The present invention further provides a compound of formula 1 in which $R^1$ and $R^2$ are taken together with the atom(s) to which they are attached to form a -($C_2$-$C_9$)heterocyclyl optionally substituted by one to three moieties selected from the group consisting of a hydrogen, halogen, hydroxy, -$NO_2$, -CN, -($C_1$-$C_6$)alkyl, -($C_2$-$C_6$)alkenyl, -($C_2$-$C_6$)alkynyl, -C=N-OH, -C=N-O($C_1$-$C_6$ alkyl), -$NR^5R^6$, -$OR^5$, -($C_3$-$C_7$)cycloalkyl, -($C_2$-$C_9$)heterocyclyl, -$CO_2R^5$, -$CONR^5R^6$, -$CONR^5R^8$, -$SR^7$, -$SOR^7$, -$SO_2R^7$, -$SO_2NR^5R^6$, -$NHCOR^5$, -$NR^5CONR^5R^6$, and -$NR^5SO_2R^7$, wherein said –($C_2$-$C_6$)alkenyl and –($C_2$-$C_6$)alkynyl moieties of said cyclic group may be optionally substituted by one to three $R^5$ groups.

The present invention also provides a compound of formula 1 in which $R^1$ and $R^2$ are taken together with the atom(s) to which they are attached to form a -($C_3$-$C_{10}$)cycloalkyl optionally substituted by one to three moieties selected from the group consisting of a hydrogen, halogen, hydroxy, -$NO_2$, -CN, -($C_1$-$C_6$)alkyl, -($C_2$-$C_6$)alkenyl, -($C_2$-$C_6$)alkynyl, -C=N-OH, -C=N-O($C_1$-$C_6$ alkyl), -$NR^5R^6$, -$OR^5$, -($C_3$-$C_7$)cycloalkyl, -($C_2$-$C_9$)heterocyclyl, -$CO_2R^5$, -$CONR^5R^6$, -$CONR^5R^8$, -$SR^7$, -$SOR^7$, -$SO_2R^7$, -$SO_2NR^5R^6$, -$NHCOR^5$, -$NR^5CONR^5R^6$, and -$NR^5SO_2R^7$, wherein said –($C_2$-$C_6$)alkenyl and –($C_2$-$C_6$)alkynyl moieties of said cyclic group may be optionally substituted by one to three $R^5$ groups; and n is 1.

The present invention further provides a compound of formula 1 in which $R^1$ and $R^2$ are taken together with the atom(s) to which they are attached to form a -($C_2$-$C_9$)heterocyclyl optionally substituted by one to three moieties selected from the group consisting of a hydrogen, halogen, hydroxy, -$NO_2$, -CN, -($C_1$-$C_6$)alkyl, -($C_2$-$C_6$)alkenyl, -($C_2$-$C_6$)alkynyl, -C=N-OH, -C=N-O($C_1$-$C_6$ alkyl), -$NR^5R^6$, -$OR^5$, -($C_3$-$C_7$)cycloalkyl, -($C_2$-$C_9$)heterocyclyl, -$CO_2R^5$, -$CONR^5R^6$, -$CONR^5R^8$, -$SR^7$, -$SOR^7$, -$SO_2R^7$, -$SO_2NR^5R^6$, -$NHCOR^5$, -$NR^5CONR^5R^6$, and -$NR^5SO_2R^7$, wherein said –($C_2$-$C_6$)alkenyl and –($C_2$-$C_6$)alkynyl moieties of said cyclic group may be optionally substituted by one to three $R^5$ groups; and n is 1.

The present invention also provides a compound of formula 1 wherein $R^3$ is hydrogen.

Preferably, $R^3$ is -($C_6$-$C_{10}$)aryl or -($C_1$-$C_9$)heteroaryl, optionally substituted by one to three moieties independently selected from the group consisting of halogen, hydroxy, -($C_1$-$C_6$)alkyl, -($C_1$-$C_6$)alkyl-P(O)(O($C_1$-$C_6$)alkyl)$_2$, -($C_3$-$C_{10}$)cycloalkyl, ($C_6$-$C_{10}$)aryl, ($C_2$-$C_9$)heterocyclyl, -($C_1$-$C_9$)heteroaryl, -$NR^5R^6$, -$NHSO_2$($C_1$-$C_6$)alkyl, -$NHSO_2$($C_3$-$C_6$)cycloalkyl, -N(($C_1$-$C_6$)alkyl)($SO_2$-$C_1$-$C_6$)alkyl), -N(($C_1$-$C_6$)alkyl)($SO_2$($C_3$-$C_6$)cycloalkyl), -O($C_1$-$C_6$)alkyl, -O-$SO_2$($C_1$-$C_6$)alkyl, -(CO)($C_1$-$C_6$)alkyl, -(CO)$CF_3$, -(CO)($C_3$-$C_{10}$)cycloalkyl, -(CO)($C_6$-$C_{10}$)aryl, -(CO)($C_2$-$C_9$)heterocyclyl, -(CO)($C_1$-$C_9$)heteroaryl, -(CO)O($C_1$-$C_6$)alkyl, -(CO)O($C_3$-$C_{10}$)cycloalkyl, -(CO)O($C_6$-$C_{10}$)aryl, -(CO)O($C_2$-$C_9$)heterocyclyl, -(CO)O($C_1$-$C_9$)heteroaryl, -(CO)($C_1$-$C_6$)alkyl-O($C_1$-$C_6$)alkyl, -$SO_2$($C_1$-$C_6$)alkyl, -$SO_2$($C_3$-$C_6$)cycloalkyl, $SO_2CF_3$, $SO_2NH_2$, $SO_2NH$($C_1$-$C_6$)alkyl, -$SO_2NH$($C_3$-$C_6$)cycloalkyl,

$-SO_2N((C_1-C_6)alkyl)_2$, $-SO_2N((C_3-C_6)cycloalkyl)_2$, $-SO_2NR^5R^6$, and $-SO_2N(C_1-C_6)alkyl-(C_6-C_{10})aryl$; wherein said $-(C_6-C_{10})$ aryl or $-(C_1-C_9)$ heteroaryl are optionally interrupted by one to three elements selected from the group consisting of –(C=O), $-SO_2$, -S-, -O-, -N-, -NH- and $-NR^5$; and $R^5$ and $R^6$ of said $NR^5R^6$ $R^3$(b) group may be taken together with the atoms to which they are attached to form a $-(C_2-C_9)$heterocyclyl.

Alternatively, the invention provides a compound of formula 1 wherein $R^3$ is $-(C_6-C_{10})$aryl, optionally substituted by one to three moieties independently selected from the group consisting of halogen, hydroxy, $-(C_1-C_6)$alkyl, $-(C_3-C_{10})$cycloalkyl, $-NHSO_2(C_1-C_6)$alkyl, $-NHSO_2(C_3-C_6)$cycloalkyl , $-N((C_1-C_6)alkyl)(SO_2-C_1-C_6)alkyl)$, $-N((C_1-C_6)alkyl)(SO_2(C_3-C_6)cycloalkyl)$, $-O(C_1-C_6)$alkyl, $-O-SO_2(C_1-C_6)$alkyl, $-SO_2(C_1-C_6)$alkyl, $-SO_2(C_3-C_6)$cycloalkyl, $-SO_2NH_2$, $-SO_2NH(C_1-C_6)$alkyl, $-SO_2NH(C_3-C_6)$cycloalkyl, $-SO_2N((C_1-C_6)alkyl)_2$, $-SO_2N((C_3-C_6)cycloalkyl)_2$, and $-SO_2NR^5R^6$.

The invention also provides a compound of formula 1 wherein $R^3$ is $-(C_1-C_9)$heteroaryl, optionally substituted by one to three moieties independently selected from the group consisting of halogen, hydroxy, $-(C_1-C_6)$alkyl, $-(C_3-C_{10})$cycloalkyl, $-NHSO_2(C_1-C_6)$alkyl, $-NHSO_2(C_3-C_6)$cycloalkyl , $-N((C_1-C_6)alkyl)(SO_2-C_1-C_6)alkyl)$, $-N((C_1-C_6)alkyl)(SO_2(C_3-C_6)cycloalkyl)$, $-O(C_1-C_6)$alkyl, $-O-SO_2(C_1-C_6)$alkyl, $-SO_2(C_1-C_6)$alkyl, $-SO_2(C_3-C_6)$cycloalkyl, $-SO_2NH_2$, $-SO_2NH(C_1-C_6)$alkyl, $-SO_2NH(C_3-C_6)$cycloalkyl, $-SO_2N((C_1-C_6)alkyl)_2$, $-SO_2N((C_3-C_6)cycloalkyl)_2$, and $-SO_2NR^5R^6$.

Further, the invention provides a compound in which $R^3$ is selected from $-(C_3-C_{10})$cycloalkyl, $-(C_2-C_9)$heterocyclyl, and $-(C_1-C_6)$alkyl-$(C_2-C_9)$ heterocyclyl, optionally substituted by one to three moieties independently selected from the group consisting of halogen, hydroxy, $-(C_1-C_6)$alkyl, $-(C_1-C_6)alkyl-P(O)(O(C_1-C_6)alkyl)_2$, $-(C_3-C_{10})$cycloalkyl, $(C_6-C_{10})$aryl, $(C_2-C_9)$heterocyclyl, $-(C_1-C_9)$heteroaryl, $-NR^5R^6$, $-NSO_2(C_1-C_6)$alkyl, $-NHSO_2(C_3-C_6)$cycloalkyl, $-N((C_1-C_6)alkyl)(SO_2-C_1-C_6)alkyl)$, $-N((C_1-C_6)alkyl)(SO_2(C_3-C_6)cycloalkyl)$, $-O(C_1-C_6)$alkyl, $-O-SO_2(C_1-C_6)$alkyl, $-O-SO_2(C_1-C_6)$alkyl, $-(CO)(C_1-C_6)$alkyl, $-(CO)CF_3$, $-(CO)(C_3-C_{10})$cycloalkyl, $-(CO)(C_6-C_{10})$aryl, $-(CO)(C_2-C_9)$heterocyclyl, $-(CO)(C_1-C_9)$heteroaryl, $-(CO)O(C_1-C_6)$alkyl, $-(CO)O(C_3-C_{10})$cycloalkyl, $-(CO)O(C_6-C_{10})$aryl, $-(CO)O(C_2-C_9)$heterocyclyl, $-(CO)O(C_1-C_9)$heteroaryl, $-(CO)(C_1-C_6)alkyl-O(C_1-C_6)$alkyl, $-SO_2(C_1-C_6)$alkyl, $-SO_2(C_3-C_6)$cycloalkyl, $SO_2CF_3$, $SO_2NH_2$, $SO_2NH(C_1-C_6)$alkyl, $-SO_2NH(C_3-C_6)$cycloalkyl, $-SO_2N((C_1-C_6)alkyl)_2$, $-SO_2N((C_3-C_6)cycloalkyl)_2$, $-SO_2NR^5R^6$, and $-SO_2N(C_1-C_6)alkyl-(C_6-C_{10})aryl$; wherein said $-(C_3-C_{10})$cycloalkyl, $-(C_2-C_9)$heterocyclyl, and $-(C_1-C_6)$alkyl-$(C_2-C_9)$ heterocyclyl are optionally interrupted by one to three elements selected from the group consisting of –(C=O), $-SO_2$, -S-, -O-, -N-, -NH- and $-NR^5$; and $R^5$ and $R^6$ of

said $NR^5R^6$ $R^3$(b) group may be taken together with the atoms to which they are attached to form a -($C_2$-$C_9$)heterocyclyl.

Also provided is a compound in which $R^3$ is -($C_3$-$C_{10}$)cycloalkyl, optionally substituted by one to three moieties independently selected from the group consisting of halogen, hydroxy, -($C_1$-$C_6$)alkyl, -($C_3$-$C_{10}$)cycloalkyl, -$NSO_2$($C_1$-$C_6$)alkyl, -$NHSO_2$($C_3$-$C_6$)cycloalkyl, -N(($C_1$-$C_6$)alkyl)($SO_2$-$C_1$-$C_6$)alkyl), -N(($C_1$-$C_6$)alkyl)($SO_2$($C_3$-$C_6$)cycloalkyl), -O($C_1$-$C_6$)alkyl, -O-$SO_2$($C_1$-$C_6$)alkyl, -$SO_2$($C_1$-$C_6$)alkyl, -$SO_2$($C_3$-$C_6$)cycloalkyl, $SO_2NH_2$, $SO_2NH$($C_1$-$C_6$)alkyl, -$SO_2NH$($C_3$-$C_6$)cycloalkyl, -$SO_2N$(($C_1$-$C_6$)alkyl)$_2$, -$SO_2N$(($C_3$-$C_6$)cycloalkyl)$_2$, and -$SO_2NR^5R^6$.

The invention further provides a compound in which $R^3$ is -($C_2$-$C_9$)heterocyclyl, optionally substituted by one to three moieties independently selected from the group consisting of halogen, hydroxy, -($C_1$-$C_6$)alkyl, -($C_3$-$C_{10}$)cycloalkyl, -$NSO_2$($C_1$-$C_6$)alkyl, -$NHSO_2$($C_3$-$C_6$)cycloalkyl, -N(($C_1$-$C_6$)alkyl)($SO_2$-$C_1$-$C_6$)alkyl), -N(($C_1$-$C_6$)alkyl)($SO_2$($C_3$-$C_6$)cycloalkyl), -O($C_1$-$C_6$)alkyl, -O-$SO_2$($C_1$-$C_6$)alkyl, -$SO_2$($C_1$-$C_6$)alkyl, -$SO_2$($C_3$-$C_6$)cycloalkyl, $SO_2NH_2$, $SO_2NH$($C_1$-$C_6$)alkyl, -$SO_2NH$($C_3$-$C_6$)cycloalkyl, -$SO_2N$(($C_1$-$C_6$)alkyl)$_2$, -$SO_2N$(($C_3$-$C_6$)cycloalkyl)$_2$, and -$SO_2NR^5R^6$.

The invention further provides a compound in which $R^3$ is -($C_1$-$C_6$)alkyl-($C_2$-$C_9$) heterocyclyl, optionally substituted by one to three moieties independently selected from the group consisting of halogen, hydroxy, -($C_1$-$C_6$)alkyl, -($C_3$-$C_{10}$)cycloalkyl, -$NSO_2$($C_1$-$C_6$)alkyl, -$NHSO_2$($C_3$-$C_6$)cycloalkyl, -N(($C_1$-$C_6$)alkyl)($SO_2$-$C_1$-$C_6$)alkyl), -N(($C_1$-$C_6$)alkyl)($SO_2$($C_3$-$C_6$)cycloalkyl), -O($C_1$-$C_6$)alkyl, -O-$SO_2$($C_1$-$C_6$)alkyl, -$SO_2$($C_1$-$C_6$)alkyl, -$SO_2$($C_3$-$C_6$)cycloalkyl, $SO_2NH_2$, $SO_2NH$($C_1$-$C_6$)alkyl, -$SO_2NH$($C_3$-$C_6$)cycloalkyl, -$SO_2N$(($C_1$-$C_6$)alkyl)$_2$, -$SO_2N$(($C_3$-$C_6$)cycloalkyl)$_2$, and -$SO_2NR^5R^6$.

Moreover, the invention provides a compound of formula 1 wherein $R^3$ is -($C_1$-$C_6$)alkyl optionally substituted by one to three moieties selected from the group consisting of halogen, hydroxy, -($C_1$-$C_6$)alkyl, -($C_1$-$C_6$)alkyl-P(O)(O($C_1$-$C_6$)alkyl)$_2$, -($C_3$-$C_{10}$)cycloalkyl, ($C_6$-$C_{10}$)aryl, ($C_2$-$C_9$)heterocyclyl, -($C_1$-$C_9$)heteroaryl, -$NR^5R^6$, -$NSO_2$($C_1$-$C_6$)alkyl, -$NHSO_2$($C_3$-$C_6$)cycloalkyl, -N(($C_1$-$C_6$)alkyl)($SO_2$-$C_1$-$C_6$)alkyl), -N(($C_1$-$C_6$)alkyl)($SO_2$($C_3$-$C_6$)cycloalkyl), -O($C_1$-$C_6$)alkyl, -O-$SO_2$($C_1$-$C_6$)alkyl, -(CO)($C_1$-$C_6$)alkyl, -(CO)$CF_3$, -(CO)($C_3$-$C_{10}$)cycloalkyl, -(CO)($C_6$-$C_{10}$)aryl, -(CO)($C_2$-$C_9$)heterocyclyl, -(CO)($C_1$-$C_9$)heteroaryl, -(CO)O($C_1$-$C_6$)alkyl, -(CO)O($C_3$-$C_{10}$)cycloalkyl, -(CO)O($C_6$-$C_{10}$)aryl, -(CO)O($C_2$-$C_9$)heterocyclyl, -(CO)O($C_1$-$C_9$)heteroaryl, -(CO)($C_1$-$C_6$)alkyl-O($C_1$-$C_6$)alkyl, -$SO_2$($C_1$-$C_6$)alkyl, -$SO_2$($C_3$-$C_6$)cycloalkyl, $SO_2CF_3$, $SO_2NH_2$, $SO_2NH$($C_1$-$C_6$)alkyl, -$SO_2NH$($C_3$-$C_6$)cycloalkyl, -$SO_2N$(($C_1$-$C_6$)alkyl)$_2$, -$SO_2N$(($C_3$-$C_6$)cycloalkyl)$_2$, -$SO_2NR^5R^6$, and -$SO_2N$($C_1$-$C_6$)alkyl-($C_6$-$C_{10}$)aryl; wherein said -($C_1$-$C_6$)alkyl is optionally interrupted by one to three elements selected from the group consisting of –(C=O), -$SO_2$, -S-, -O-, -N-, -NH- and

$-NR^5$; and $R^5$ and $R^6$ of said $NR^5R^6$ $R^3$(b) group may be taken together with the atoms to which they are attached to form a $-(C_2-C_9)$heterocyclyl.

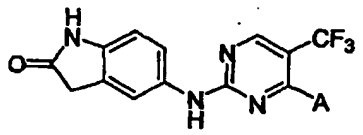
Further provided is a compound of formula 1 wherein $R^3$ is $-(C_1-C_6)$alkyl optionally substituted by one to three moieties selected from the group consisting of halogen, hydroxy, $-(C_1-C_6)$alkyl, $-(C_3-C_{10})$cycloalkyl, $-NSO_2(C_1-C_6)$alkyl, $-NHSO_2(C_3-C_6)$cycloalkyl, $-N((C_1-C_6)alkyl)(SO_2-C_1-C_6)alkyl)$, $-N((C_1-C_6)alkyl)(SO_2(C_3-C_6)cycloalkyl)$, $-O(C_1-C_6)$alkyl, $-O-SO_2(C_1-C_6)$alkyl, $-SO_2(C_1-C_6)$alkyl, $-SO_2(C_3-C_6)$cycloalkyl, $-SO_2NH_2$, $SO_2NH(C_1-C_6)$alkyl, $-SO_2NH(C_3-C_6)$cycloalkyl, $-SO_2N((C_1-C_6)alkyl)_2$, $-SO_2N((C_3-C_6)cycloalkyl)_2$, and $-SO_2NR^5R^6$.

In a preferred embodiment, $R^4$ is a substituent selected from the group consisting of hydrogen, $(C_1-C_6)$alkyl, and $-(C_3-C_7)$cycloalkyl; wherein said $-(C_1-C_6)$alkyl and $-(C_3-C_7)$cycloalkyl is optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, $-(C_1-C_6)$alkyl, -CN, $-NR^5_2$, $-OR^5$, $-(C_3-C_7)$cycloalkyl, $-(C_2-C_9)$heterocyclyl, $-CO_2R^5$, and $-CONR^5R^6$; with the proviso that a heteroatom of the foregoing $R^4$ substituents may not be bound to an $sp^3$ carbon atom bound to another heteroatom; and wherein $R^5$ and $R^6$ of said $-CONR^5R^6$ group may be taken together with the atoms to which they are attached to form a $-(C_2-C_9)$heterocyclyl.

In a further preferred embodiment, $R^4$ is hydrogen.

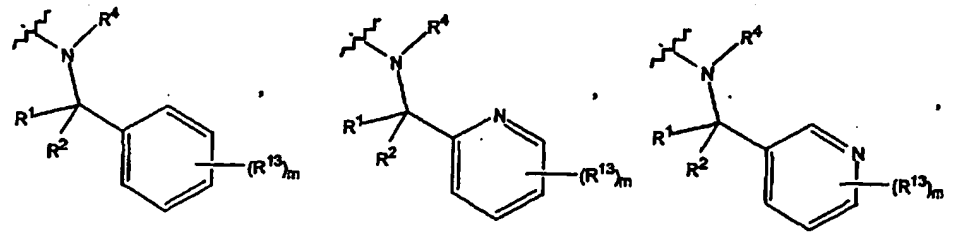
Further, the invention provides a compound of formula 1 wherein $R^5$ and $R^6$ are each substituents independently selected from the group consisting of hydrogen and $-(C_1-C_6)$alkyl, optionally substituted as described above.

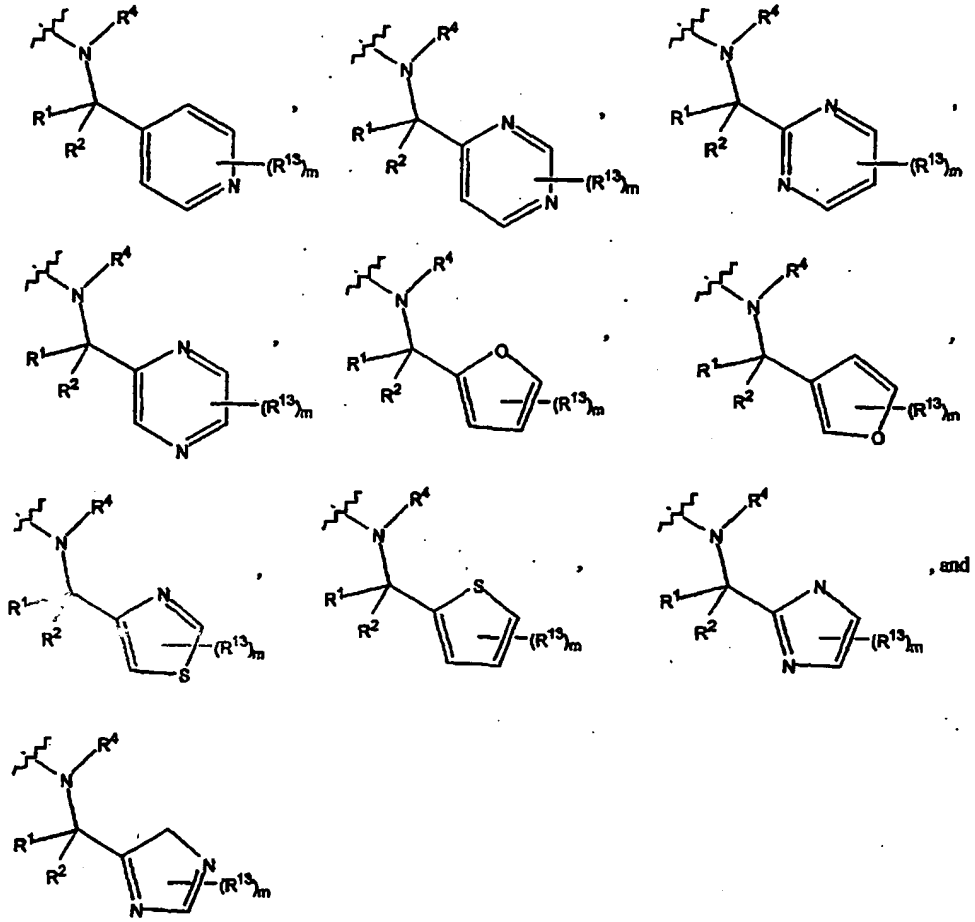
In a preferred embodiment, the present invention provides a compound of the formula 2



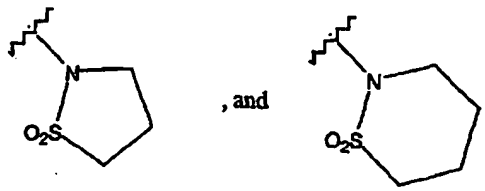
2

wherein A is selected from the group consisting of:

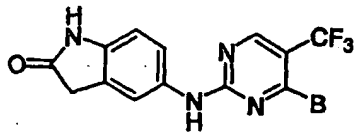




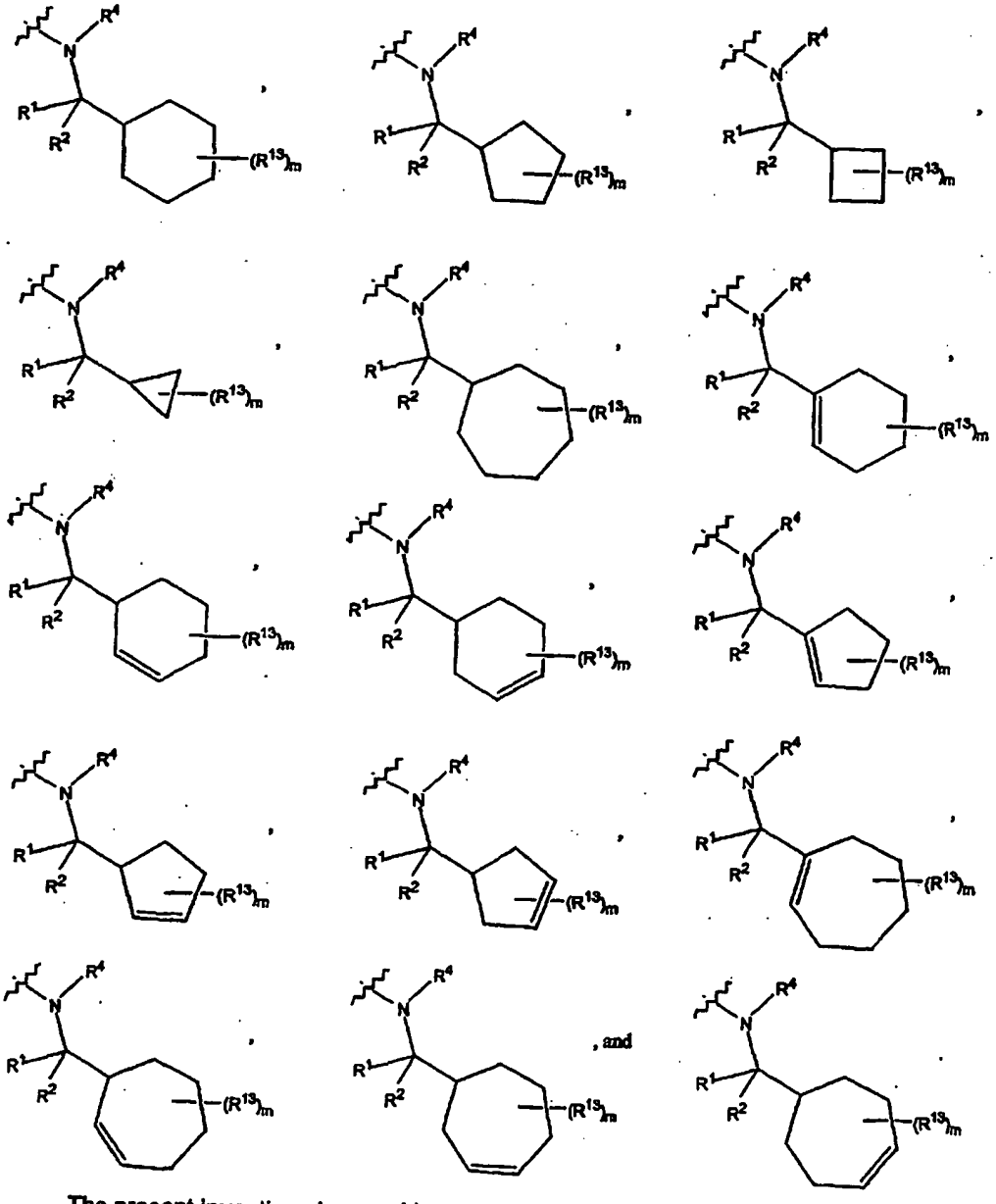
wherein m is an integer from 0-3 and $R^{13}$ is a substituent selected from the group consisting of hydrogen, halogen, hydroxy, $(C_1-C_6)$-alkyl, $(C_3-C_7)$-cycloalkyl, $(C_6-C_{10})$-aryl, $(C_1-C_9)$heteroaryl, $(C_2-C_9)$-heterocyclyl, O-$(C_1-C_6)$-alkyl, O-$(C_3-C_7)$-cycloalkyl, $SO_2$-$(C_1-C_6)$alkyl, $SO_2(C_3-C_7)$-cycloalkyl, $NHSO_2(C_1-C_6)$alkyl, $N((C_1-C_6)alkyl)(SO_2(C_1-C_6-alkyl))$, $N((C_3-C_7)cycloalkyl)(SO_2(C_1-C_6-alkyl))$, $N(C_1-C_6-alkyl)(SO_2(C_3-C_7)cycloalkyl)$, $N((C_3-C_7)cycloalkyl)(SO_2(C_3-C_7)cycloalkyl)$, $OSO_2(C_1-C_6)alkyl$, $SO_2CF_3$, $SO_2NH_2$, $SO_2NH(C_1-C_6)alkyl$, $SO_2NH(C_3-C_7)cycloalkyl$, $SO_2NR^5R^6$, $SO_2N((C_1-C_6)alkyl)_2$, $CF_3$, CO-$(C_1-C_6)$alkyl, CO-$(C_3-C_7)$cycloalkyl, $COCF_3$, $CO_2(C_1-C_6)alkyl$,



Also provided is a compound of the formula 3

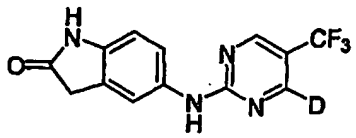


wherein B is selected from the group consisting of:

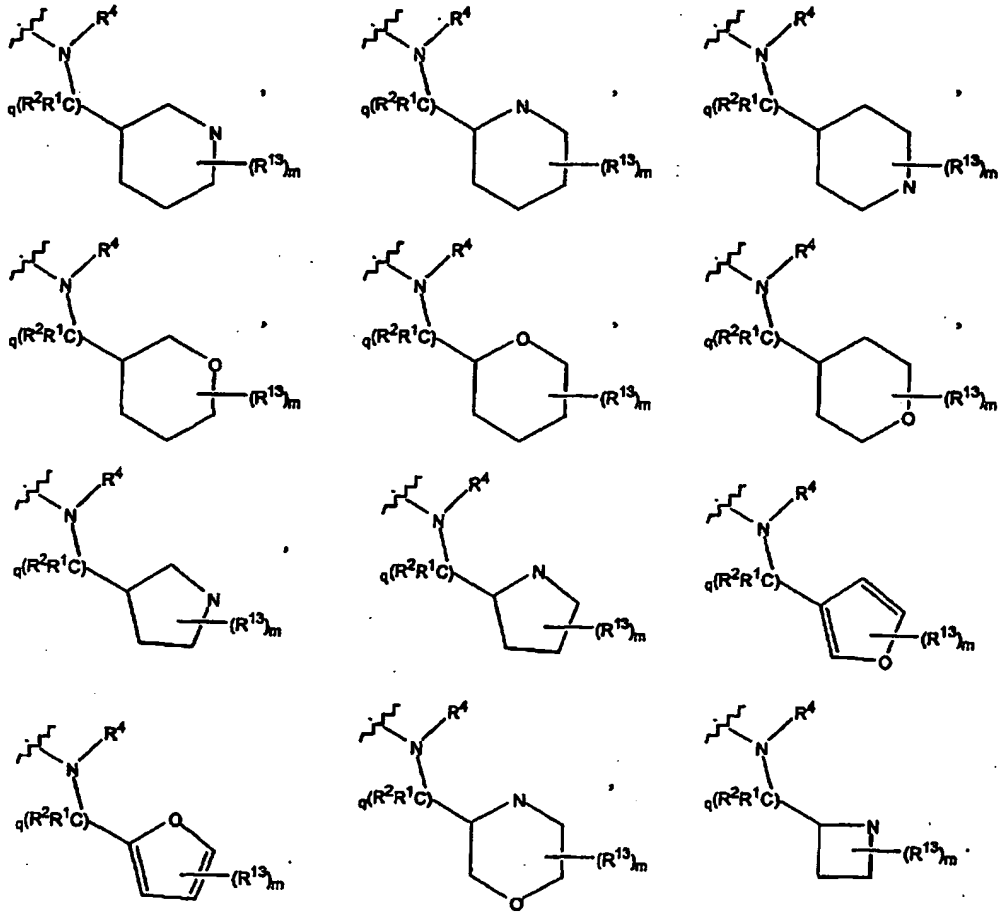


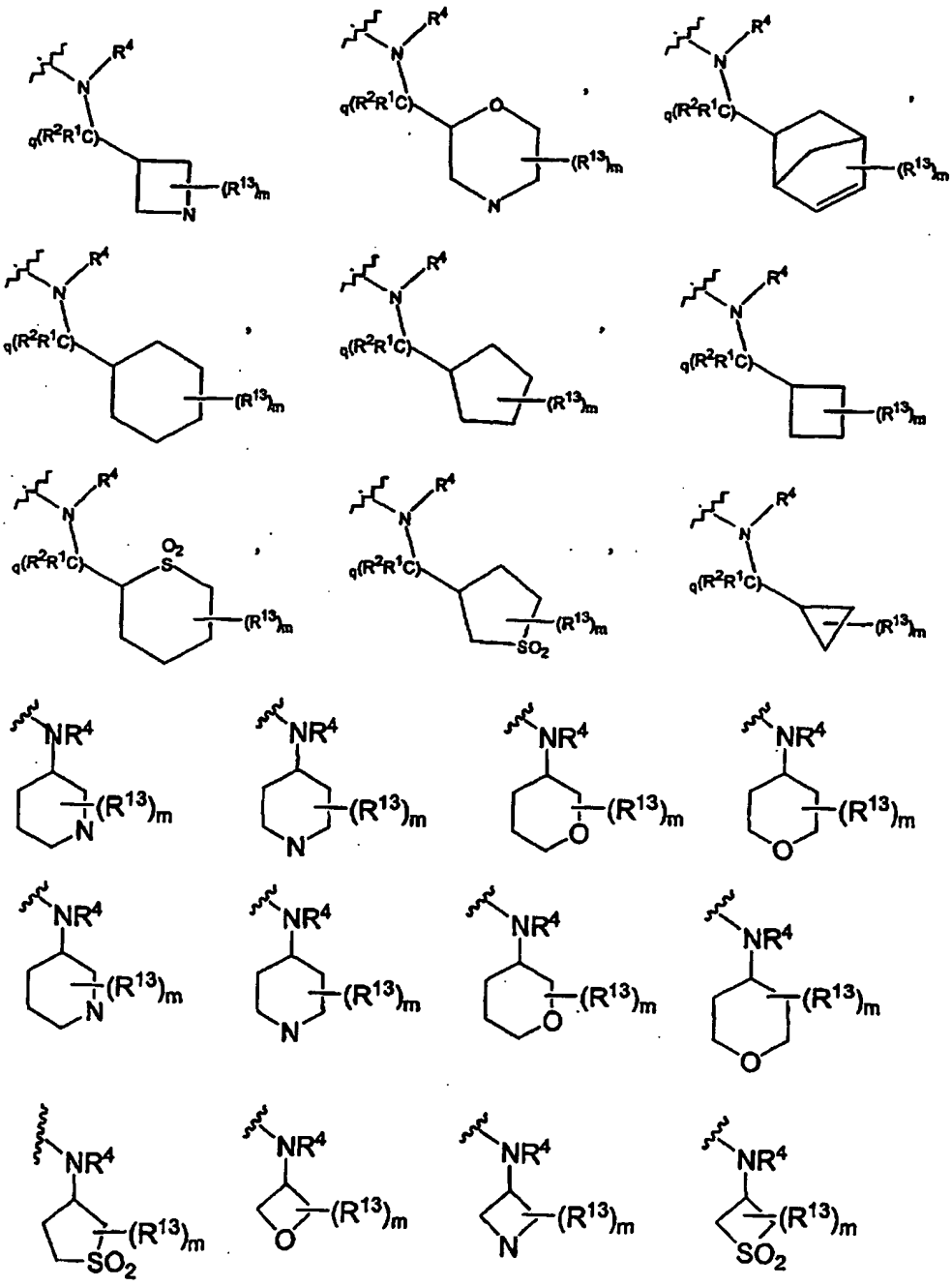
, and

The present invention also provides a compound of formula 4



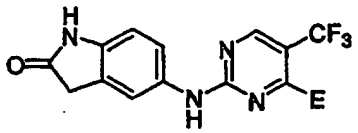
wherein D is selected from the group consisting of:



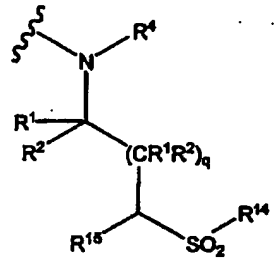


wherein q is an integer from 1-2.

Moreover, the present invention provides a compound of formula 5:



wherein E is selected from the group consisting of:



wherein $R^{14}$ is selected from the group consisting of $(C_1-C_6)$-alkyl, $(C_3-C_7)$-cycloalkyl, and $(C_2-C_9)$-heterocyclyl, and $R^{15}$ is selected from the group consisting of hydrogen, $(C_1-C_6)$-alkyl, $(C_3-C_7)$-cycloalkyl, and $(C_2-C_9)$-heterocyclyl.

Specific embodiments of the present invention are compounds selected from

N-(1-Methyl-1-phenyl-ethyl)-3-{[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-methyl}-benzenesulfonamide;

3-{[2-(2-Oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-methyl}-benzenesulfonamide;

5-{4-[3-(Trifluoro-methanesulfonyl)-benzylamino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-{4-[(Piperidin-3-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-{4-[(1-Methanesulfonyl-piperidin-3-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

N-(3-{[2-(2-Oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-methyl}-phenyl)-methanesulfonamide;

3-Oxo-3-(3-{[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-methyl}-piperidin-1-yl)-propionitrile;

5-{4-[3-(1,1-Dioxo-1N$^6$-isothiazolidin-2-yl)-propylamino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-[4-(2-Methyl-butylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-{4-[(1-Methanesulfonyl-piperidin-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

N-{2-[2-(2-Oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-ethyl}-methanesulfonamide;

N-{4-[2-(2-Oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-butyl}-methanesulfonamide;

5-{4-[(1-Methanesulfonyl-piperidin-4-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

N-Methyl-N-{2-[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-ethyl}-methanesulfonamide;

Methanesulfonic acid 3-{[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-methyl}-phenyl ester;

N-{3-[2-(2-Oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-propyl}-methanesulfonamide;

5-{4-[(4-Methanesulfonyl-morpholin-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

N-(4-Fluoro-3-{[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-methyl}-phenyl)-methanesulfonamide;

5-{4-[(5-Oxo-morpholin-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one

N-(4-Methoxy-3-{[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-methyl}-phenyl)-methanesulfonamide;

N-(4-Methyl-3-{[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-methyl}-phenyl)-methanesulfonamide;

5-[4-(3-Methanesulfonylmethyl-benzylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-{4-[(4-Trifluoroacetyl-morpholin-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-{4-[(1-Methanesulfonyl-azetidin-3-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

N-Methyl-N-(4-methyl-3-{[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-methyl}-phenyl)-methanesulfonamide;

5-{4-[(1-Methanesulfonyl-pyrrolidin-3-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

N-Methyl-N-{3-[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-propyl}-methanesulfonamide;

5-{4-[2-(1-Methanesulfonyl-piperidin-2-yl)-ethylamino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-{4-[(4-Methanesulfonyl-pyridin-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

{2,2-Dimethyl-3-[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-propyl}-carbamic acid tert-butyl ester;

5-[4-(3-Isopropoxy-propylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-{4-[(1-Methyl-piperidin-3-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-{4-[(Tetrahydro-pyran-4-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-[4-(2-Ethyl-butylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-{4-[(Tetrahydro-furan-2R-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-{4-[(Tetrahydro-furan-2S-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-{4-[(5-Methyl-furan-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-{4-[(1-Methanesulfonyl-pyrrolidin-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-{4-[(Adamantan-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-{4-[(Adamantan-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-[4-(2-Methoxy-2-methyl-propylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-{4-[(*endo*-Bicyclo[2.2.1]hept-5-en-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

(3-{[2-(2-Oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-methyl}-benzyl)-phosphonic acid dimethyl ester;

5-[4-(3-Methyl-butylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-{4-[(2-Hydroxy-cyclohexylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

N-(4-Methoxy-3-{[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-methyl}-phenyl)-N-methyl-methanesulfonamide;

5-{4-[(4-Ethanesulfonyl-morpholin-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-(4-[[4-(Propane-2-sulfonyl)-morpholin-2-ylmethyl]-amino}-5-trifluoromethyl-pyrimidin-2-ylamino)-1,3-dihydro-indol-2-one;

5-{4-[(4-Acetyl-morpholin-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-{4-[(4-Propionyl-morpholin-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-(4-[[4-(2,2-Dimethyl-propionyl)-morpholin-2-ylmethyl]-amino}-5-trifluoromethyl-pyrimidin-2-ylamino)-1,3-dihydro-indol-2-one;

2-[[2-(2-Oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-methyl}-morpholine-4-carboxylic acid methyl ester;

5-{4-[(4-Methoxyacetyl-morpholin-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-[4-(3-Ethanesulfonyl-benzylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-{4-[(4-Methanesulfonyl-morpholin-2R-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-{4-[(4-Methanesulfonyl-morpholin-2S-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-{4-[(Pyrimidin-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-{4-[(Pyrazin-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

N-(4-Fluoro-3-{[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-methyl}-phenyl)-N-methyl-methanesulfonamide;

5-{4-[(1-Methanesulfonyl-piperidin-3-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-{4-[(4-Isobutyryl-morpholin-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-[4-(3,3-Dimethyl-2-oxo-butylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-[4-(1,2-Dimethyl-propylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-[4-(2-Methoxy-1-methyl-ethylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-{4-[2-(1,1-Dioxo-1D$^{6}$-isothiazolidin-2-yl)-ethylamino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-[4-(3-Methylamino-propylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-{4-[(Pyridin-3-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-{4-[(6-Methanesulfonyl-pyridin-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-{4-[3-(1,1-Dioxo-1,l,6-isothiazolidin-2-yl)-benzylamino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-[4-(1R-Phenyl-ethylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-(4-Isopropylamino-5-trifluoromethyl-pyrimidin-2-ylamino)-1,3-dihydro-indol-2-one;

5-(4R-sec-Butylamino-5-trifluoromethyl-pyrimidin-2-ylamino)-1,3-dihydro-indol-2-one;

5-(4S-sec-Butylamino-5-trifluoromethyl-pyrimidin-2-ylamino)-1,3-dihydro-indol-2-one;

5-[4-(2-Methylamino-ethylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-[4-(1S-Phenyl-ethylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-{4-[(2-Methanesulfonylmethyl-thiazol-4-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-(4-Propylamino-5-trifluoromethyl-pyrimidin-2-ylamino)-1,3-dihydro-indol-2-one;

5-[4-(2-Hydroxy-1-methyl-ethylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-[4-(1-Hydroxymethyl-propylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-{4-[(5-Methanesulfonyl-pyridin-3-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-{4-[(Pyridin-4-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-[4-(1,3-Dimethyl-butylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

N-Isopropyl-N-{3-[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-propyl}-methanesulfonamide;

5-[4-(1S-Hydroxymethyl-2-methyl-propylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

N-Cyclohexyl-N-{3-[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-propyl}-methanesulfonamide;

5-[4-(1,2,3,4-Tetrahydro-naphthalen-1-ylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-{4-[(1-Methanesulfonyl-pyrrolidin-2S-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-{4-[(3-Methyl-thiophen-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-{4-[(1-Methanesulfonyl-pyrrolidin-3R-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-[4-(2-Hydroxy-1S-phenyl-ethylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-[4-(2-Hydroxy-1S-methyl-ethylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-[4-(1R-Hydroxymethyl-propylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-[4-(1-Pyrimidin-4-yl-ethylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-[4-(1,1-Dioxo-tetrahydro-1-thiophen-3-ylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-{4-[(1H-Imidazol-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-[4-(2-Piperidin-2-yl-ethylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-[4-(Isobutyl-methyl-amino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

N-Methyl-N-(3-{[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-methyl}-phenyl)-methanesulfonamide;

N-Ethyl-N-(3-{[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-methyl}-phenyl)-methanesulfonamide;

5-[4-(2-Methanesulfonyl-benzylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

N-Isopropyl-N-(3-{[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-methyl}-phenyl)-methanesulfonamide;

5-[4-[(3,4,5,6-Tetrahydro-2H-[1,2']bipyridinyl-3-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-{4-[(1-Pyrimidin-2-yl-piperidin-3-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-{4-[2R-(1-Methanesulfonyl-piperidin-2-yl)-ethylamino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-{4-[2S-(1-Methanesulfonyl-piperidin-2-yl)-ethylamino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-[4-(3-Methylsulfanyl-propylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-[4-(1S-Hydroxymethyl-3-methylsulfanyl-propylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-[4-(2-Hydroxy-1R-methyl-ethylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-[4-(1R-Hydroxymethyl-2-methyl-propylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

N-Ethyl-N-{3-[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-propyl}-methanesulfonamide;

5-{4-[(1-Methanesulfonyl-pyrrolidin-3R-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-[4-(1S-Hydroxymethyl-propylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-[4-(3,5-Dinitro-benzylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

N-(2-{[2-(2-Oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-methyl}-phenyl)-methanesulfonamide;

N-Isopropyl-N-{2-[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-ethyl}-methanesulfonamide;

5-[4-(2-Hydroxy-1-phenyl-ethylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-[4-(1R-Hydroxymethyl-3-methyl-butylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-[4-(1S-Hydroxymethyl-3-methyl-butylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-{4-[(1-Methanesulfonyl-piperidin-2S-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-{4-[(1-Methanesulfonyl-pyrrolidin-2R-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-[4-(Methyl-pyridin-2-ylmethyl-amino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-{4-[(3-Methanesulfonyl-benzyl)-methyl-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

N-Methyl-N-(2-{[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-methyl}-phenyl)-methanesulfonamide;

5-[4-(Methyl-pyridin-3-ylmethyl-amino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-{4-[(1-Methanesulfonyl-piperidin-3-ylmethyl)-methyl-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-[4-(Methyl-pyridin-4-ylmethyl-amino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-(4-Cyclopentylamino-5-trifluoromethyl-pyrimidin-2-ylamino)-1,3-dihydro-indol-2-one;

5-[4-(2,6-Dimethoxy-benzylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-{4-[(1,5-Dimethyl-1H-pyrazol-3-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one and

5-[4-(2-Imidazol-1-yl-ethylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one.

Certain preferred embodiments of the invention are compounds selected from:

5-{4-[(1-Methanesulfonyl-piperidin-3-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

N-Methyl-N-(2-[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-ethyl)-methanesulfonamide;

N-Methyl-N-(3-[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-propyl)-methanesulfonamide;

5-{4-[2-(1-Methanesulfonyl-piperidin-2-yl)-ethylamino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-{4-[(Bicyclo[2.2.1]hept-5-en-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-[4-(3-Methyl-butylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-{4-[(1-Methanesulfonyl-piperidin-3-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

N-Isopropyl-N-{3-[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-propyl}-methanesulfonamide;

N-Cyclohexyl-N-{3-[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-propyl}-methanesulfonamide;

5-{4-[2-(1-Methanesulfonyl-piperidin-2-yl)-ethylamino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

N-Isopropyl-N-{2-[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-ethyl}-methanesulfonamide;

5-{4-[(1-Methanesulfonyl-pyrrolidin-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-(4-Cyclopentylamino-5-trifluoromethyl-pyrimidin-2-ylamino)-1,3-dihydro-indol-2-one;

Ethanesulfonic acid methyl-{3-[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-propyl}-amide;

2,2,2-Trifluoro-N-methyl-N-{3-[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-propyl}-acetamide;

N-Methyl-N-{2-[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-ethyl}-methanesulfonamide;

5-(4-Cyclobutylamino-5-trifluoromethyl-pyrimidin-2-ylamino)-1,3-dihydro-indol-2-one;

5-{4-[2-Hydroxy-2-(1-methanesulfonyl-piperidin-2-yl)-ethylamino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

3-Oxo-3-(3-{[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-methyl}-piperidin-1-yl)-propionitrile;

5-{4-[(1-Methanesulfonyl-piperidin-4-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-{4-[(4-Methanesulfonyl-morpholin-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-{4-[(5-Oxo-morpholin-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-{4-[(1-Methanesulfonyl-pyrrolidin-3-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-[4-(3-Isopropoxy-propylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-{4-[(Adamantan-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

N-{2,2-Dimethyl-3-[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-propyl}-methanesulfonamide;

5-{4-[(1-Hydroxy-cyclopentylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-{4-[(4-Hydroxy-tetrahydro-pyran-4-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-{4-[(2-Hydroxy-cyclohexylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-[4-(3-Methanesulfonyl-propylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-{4-[(1-Pyrimidin-2-yl-piperidin-3-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

3-[2-(2-Oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-propionic acid ethyl ester;

5-{4-[(1-Ethyl-5-oxo-pyrrolidin-3-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

2,N-Dimethyl-N-{2-[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-ethyl}-butyramide;

2-Methoxy-N-methyl-N-{3-[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-propyl}-acetamide;

5-{4-[2-(1-Acetyl-piperidin-2-yl)-ethylamino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-{4-[(1-Methanesulfonyl-piperidin-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-{4-[(1-Methanesulfonyl-pyrrolidin-3-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-{4-[(1-Pyrimidin-2-yl-piperidin-3-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

3-{[2-(2-Oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-methyl}-benzenesulfonamide;

N-(3-{[2-(2-Oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-methyl}-phenyl)-methanesulfonamide;

N-(4-Methoxy-3-{[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-methyl}-phenyl)-methanesulfonamide;

5-[4-(3-Methanesulfonylmethyl-benzylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

N-Methyl-N-(4-methyl-3-{[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-methyl}-phenyl)-methanesulfonamide;

5-{4-[(4-Methanesulfonyl-pyridin-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-{4-[(5-Methyl-furan-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

(3-{[2-(2-Oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-methyl}-benzyl)-phosphonic acid dimethyl ester;

5-{4-[(Pyridin-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-[5-Trifluoromethyl-4-(2-trifluoromethyl-benzylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-[4-(3-Ethanesulfonyl-benzylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-{4-[(Pyrimidin-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-{4-[(Pyrazin-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

N-(4-Fluoro-3-{[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-methyl}-phenyl)-N-methyl-methanesulfonamide;

5-{4-[(Pyridin-3-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-{4-[(6-Methanesulfonyl-pyridin-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-{4-[(2-Methanesulfonylmethyl-thiazol-4-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-{4-[(5-Methanesulfonyl-pyridin-3-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-{4-[(3-Methyl-thiophen-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-{4-[(1H-Imidazol-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

N-Methyl-N-(3-{[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-methyl}-phenyl)-methanesulfonamide;

5-[4-(2-Methanesulfonyl-benzylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

N-(2-{[2-(2-Oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-methyl}-phenyl)-methanesulfonamide;

N-Methyl-N-(2-{[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-methyl}-phenyl)-methanesulfonamide;

5-{4-[(1,5-Dimethyl-1H-pyrazol-3-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-[4-(2-Imidazol-1-yl-ethylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

N-(5-Methyl-2-{[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-methyl}-phenyl)-methanesulfonamide;

5-{4-[(3-Methyl-pyridin-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-[4-(3-Methanesulfonyl-benzylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-{4-[(Isochroman-1-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-{4-[2-(Pyridin-3-yloxy)-propylamino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-{4-[2-(6-Methyl-pyridin-2-yl)-ethylamino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-{4-[(2,3-Dihydro-benzo[1,4]dioxin-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-{4-[2-(4-Methyl-1H-imidazol-2-yl)-ethylamino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-{4-[2-(1H-Benzoimidazol-2-yl)-ethylamino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-{4-[(5-Phenyl-4H-[1,2,4]triazol-3-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-{4-[(3-Methyl-imidazo[2,1-b]thiazol-6-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

N-Methyl-N-(2-methyl-6-{[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-methyl}-phenyl)-methanesulfonamide;

N-(2-Methyl-6-{[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-methyl}-phenyl)-methanesulfonamide;

N-(3-Methanesulfonylamino-5-{[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-methyl}-phenyl)-methanesulfonamide; and

N-Methyl-N-(3-{[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-methyl}-pyridin-2-yl)-methanesulfonamide.

Preferred embodiment of the present invention are selected from

5-[4-(3-Methanesulfonyl-benzylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

Ethanesulfonic acid methyl-{3-[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-propyl}-amide;

5-{4-[(Isochroman-1-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-{4-[2-(Pyridin-3-yloxy)-propylamino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

3-{[2-(2-Oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-methyl}-benzenesulfonamide;

5-{4-[(1-Methanesulfonyl-piperidin-3-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

N-(3-{[2-(2-Oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-methyl}-phenyl)-methanesulfonamide;

N-Methyl-N-{2-[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-ethyl}-methanesulfonamide;

5-{4-[(4-Methanesulfonyl-morpholin-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-[4-(3-Methanesulfonylmethyl-benzylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-{4-[(1-Methanesulfonyl-pyrrolidin-3-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

N-Methyl-N-{3-[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-propyl}-methanesulfonamide;

5-{4-[2-(1-Methanesulfonyl-piperidin-2-yl)-ethylamino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-{4-[(4-Methanesulfonyl-pyridin-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-[4-(3-Isopropoxy-propylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-{4-[(5-Methyl-furan-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-{4-[(Bicyclo[2.2.1]hept-5-en-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

N-(4-Fluoro-3-{[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-methyl}-phenyl)-N-methyl-methanesulfonamide;

5-{4-[(1-Methanesulfonyl-piperidin-3-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-{4-[(6-Methanesulfonyl-pyridin-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-{4-[(5-Methanesulfonyl-pyridin-3-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-[4-(2-Methanesulfonyl-benzylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-{4-[(1-Pyrimidin-2-yl-piperidin-3-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-{4-[2-(1-Methanesulfonyl-piperidin-2-yl)-ethylamino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-{4-[2-(1-Methanesulfonyl-piperidin-2-yl)-ethylamino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

N-(2-{[2-(2-Oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-methyl}-phenyl)-methanesulfonamide;

5-{4-[(1-Methanesulfonyl-pyrrolidin-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

N-Methyl-N-(2-{[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-methyl}-phenyl)-methanesulfonamide;

N-Methyl-N-(2-methyl-6-{[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-methyl}-phenyl)-methanesulfonamide;

5-[4-(2-Hydroxy-indan-1-ylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-{4-[(1-Hydroxy-cyclopentylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-{4-[2-Hydroxy-2-(1-methanesulfonyl-piperidin-2-yl)-ethylamino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one; and

N-Methyl-N-(3-{[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-methyl}-pyridin-2-yl)-methanesulfonamide.

This invention also relates to a method for the treatment of abnormal cell growth in a mammal, including a human, comprising administering to said mammal an amount of a compound of the formula 1, as defined above, or a pharmaceutically acceptable salt, solvate or prodrug thereof, that is effective in treating abnormal cell growth. In one embodiment of this method, the abnormal cell growth is cancer, including, but not limited to, lung cancer, bone cancer, pancreatic cancer, skin cancer, cancer of the head or neck, cutaneous or intraocular

melanoma, uterine cancer, ovarian cancer, rectal cancer, cancer of the anal region, stomach cancer, colon cancer, breast cancer, uterine cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, Hodgkin's Disease, cancer of the esophagus, cancer of the small intestine, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the adrenal gland, sarcoma of soft tissue, cancer of the urethra, cancer of the penis, prostate cancer, chronic or acute leukemia, lymphocytic lymphomas, cancer of the bladder, cancer of the kidney or ureter, renal cell carcinoma, carcinoma of the renal pelvis, neoplasms of the central nervous system (CNS), primary CNS lymphoma, spinal axis tumors, brain stem glioma, pituitary adenoma, or a combination of one or more of the foregoing cancers. In one embodiment the method comprises comprising administering to a mammal an amount of a compound of formula 1 that is effective in treating said cancer solid tumor. In one preferred embodiment the solid tumor is breast, lung, colon, brain, prostate, stomach, pancreatic, ovarian, skin (melanoma), endocrine, uterine, testicular, and bladder cancer.

In another embodiment of said method, said abnormal cell growth is a benign proliferative disease, including, but not limited to, psoriasis, benign prostatic hypertrophy or restinosis.

This invention also relates to a method for the treatment of abnormal cell growth in a mammal which comprises administering to said mammal an amount of a compound of formula 1, or a pharmaceutically acceptable salt, solvate or prodrug thereof, that is effective in treating abnormal cell growth in combination with an anti-tumor agent selected from the group consisting of mitotic inhibitors, alkylating agents, anti-metabolites, intercalating antibiotics, growth factor inhibitors, cell cycle inhibitors, enzymes, topoisomerase inhibitors, biological response modifiers, antibodies, cytotoxics, anti-hormones, and anti-androgens.

This invention also relates to a pharmaceutical composition for the treatment of abnormal cell growth in a mammal, including a human, comprising an amount of a compound of the formula 1, as defined above, or a pharmaceutically acceptable salt, solvate or prodrug thereof, that is effective in treating abnormal cell growth, and a pharmaceutically acceptable carrier. In one embodiment of said composition, said abnormal cell growth is cancer, including, but not limited to, lung cancer, bone cancer, pancreatic cancer, skin cancer, cancer of the head or neck, cutaneous or intraocular melanoma, uterine cancer, ovarian cancer, rectal cancer, cancer of the anal region, stomach cancer, colon cancer, breast cancer, uterine cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, Hodgkin's Disease, cancer of the esophagus, cancer of the small intestine, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the adrenal gland, sarcoma of soft tissue, cancer of

the urethra, cancer of the penis, prostate cancer, chronic or acute leukemia, lymphocytic lymphomas, cancer of the bladder, cancer of the kidney or ureter, renal cell carcinoma, carcinoma of the renal pelvis, neoplasms of the central nervous system (CNS), primary CNS lymphoma, spinal axis tumors, brain stem glioma, pituitary adenoma, or a combination of one or more of the foregoing cancers. In another embodiment of said pharmaceutical composition, said abnormal cell growth is a benign proliferative disease, including, but not limited to, psoriasis, benign prostatic hypertrophy or restinosis.

The invention also relates to a pharmaceutical composition for the treatment of abnormal cell growth in a mammal, including a human, which comprises an amount of a compound of formula 1, as defined above, or a pharmaceutically acceptable salt, solvate or prodrug thereof, that is effective in treating abnormal cell growth in combination with a pharmaceutically acceptable carrier and an anti-tumor agent selected from the group consisting of mitotic inhibitors, alkylating agents, anti-metabolites, intercalating antibiotics, growth factor inhibitors, cell cycle inhibitors, enzymes, topoisomerase inhibitors, biological response modifiers, anti-hormones, and anti-androgens.

This invention also relates to a method for the treatment of a disorder associated with angiogenesis in a mammal, including a human, comprising administering to said mammal an amount of a compound of the formula 1, as defined above, or a pharmaceutically acceptable salt, solvate or prodrug thereof, that is effective in treating said disorder. Such disorders include cancerous tumors such as melanoma; ocular disorders such as age-related macular degeneration, presumed ocular histoplasmosis syndrome, and retinal neovascularization from proliferative diabetic retinopathy; rheumatoid arthritis; bone loss disorders such as osteoporosis, particularly, post-menopausal osteoporosis, Paget's disease, humoral hypercalcemia of malignancy, hypercalcemia from tumors metastatic to bone, and osteoporosis induced by glucocorticoid treatment; coronary restenosis; and certain microbial infections including those associated with microbial pathogens selected from adenovirus, hantaviruses, *Borrelia burgdorferi*, *Yersinia spp.*, *Bordetella pertussis*; and group A *Streptococcus*.

This invention also relates to a method of (and to a pharmaceutical composition for) treating abnormal cell growth in a mammal which comprise an amount of a compound of formula 1, or a pharmaceutically acceptable salt, solvate or prodrug thereof, and an amount of one or more substances selected from anti-angiogenesis agents, signal transduction inhibitors, and antiproliferative agents, which amounts are together effective in treating said abnormal cell growth.

Anti-angiogenesis agents, such as MMP-2 (matrix-metalloprotienase 2) inhibitors, MMP-9 (matrix-metalloprotienase 9) inhibitors, and COX-II (cyclooxygenase II) inhibitors, can be used in conjunction with a compound of formula 1 in the methods and pharmaceutical

compositions described herein. Examples of useful COX-II inhibitors include CELEBREX™ (alecoxib), valdecoxib, and rofecoxib. Examples of useful matrix metalloproteinase inhibitors are described in WO 96/33172 (published October 24, 1996), WO 96/27583 (published March 7, 1998), European Patent Application No. 97304971.1 (filed July 8, 1997), European Patent Application No. 99308617.2 (filed October 29, 1999), WO 98/07697 (published February 26, 1998), WO 98/03516 (published January 29, 1998), WO 98/34918 (published August 13, 1998), WO 98/34915 (published August 13, 1998), WO 98/33768 (published August 6, 1998), WO 98/30566 (published July 16, 1998), European Patent Publication 606,046 (published July 13, 1994), European Patent Publication 931,788 (published July 28, 1999), WO 90/05719 (published May 331, 1990), WO 99/52910 (published October 21, 1999), WO 99/52889 (published October 21, 1999), WO 99/29667 (published June 17, 1999), PCT International Application No. PCT/IB98/01113 (filed July 21, 1998), European Patent Application No. 99302232.1 (filed March 25, 1999), Great Britain patent application number 9912961.1 (filed June 3, 1999), United States Provisional Application No. 60/148,464 (filed August 12, 1999), United States Patent 5,863,949 (issued January 26, 1999), United States Patent 5,861,510 (issued January 19, 1999), and European Patent Publication 780,386 (published June 25, 1997), all of which are herein incorporated by reference in their entirety. Preferred MMP-2 and MMP-9 inhibitors are those that have little or no activity inhibiting MMP-1. More preferred, are those that selectively inhibit MMP-2 and/or MMP-9 relative to the other matrix-metalloproteinases (*i.e.* MMP-1, MMP-3, MMP-4, MMP-5, MMP-6, MMP-7, MMP-8, MMP-10, MMP-11, MMP-12, and MMP-13).

Some specific examples of MMP inhibitors useful in combination with the compounds of the present invention are AG-3340, RO 32-3555, RS 13-0830, and the compounds recited in the following list:

3-[[4-(4-fluoro-phenoxy)-benzenesulfonyl]-(1-hydroxycarbamoyl-cyclopentyl)-amino]-propionic acid;

3-exo-3-[4-(4-fluoro-phenoxy)-benzenesulfonylamino]-8-oxa-bicyclo[3.2.1]octane-3-carboxylic acid hydroxyamide;

(2R, 3R) 1-[4-(2-chloro-4-fluoro-benzyloxy)-benzenesulfonyl]-3-hydroxy-3-methyl-piperidine-2-carboxylic acid hydroxyamide;

4-[4-(4-fluoro-phenoxy)-benzenesulfonylamino]-tetrahydro-pyran-4-carboxylic acid hydroxyamide;

3-[[4-(4-fluoro-phenoxy)-benzenesulfonyl]-(1-hydroxycarbamoyl-cyclobutyl)-amino]-propionic acid;

4-[4-(4-chloro-phenoxy)-benzenesulfonylamino]-tetrahydro-pyran-4-carboxylic acid hydroxyamide;

3-[4-(4-chloro-phenoxy)-benzenesulfonylamino]-tetrahydro-pyran-3-carboxylic acid hydroxyamide;

(2R, 3R) 1-[4-(4-fluoro-2-methyl-benzyloxy)-benzenesulfonyl]-3-hydroxy-3-methyl-piperidine-2-carboxylic acid hydroxyamide;

3-[[4-(4-fluoro-phenoxy)-benzenesulfonyl]-(1-hydroxycarbamoyl-1-methyl-ethyl)-amino]-propionic acid;

3-[[4-(4-fluoro-phenoxy)-benzenesulfonyl]-(4-hydroxycarbamoyl-tetrahydro-pyran-4-yl)-amino]-propionic acid;

3-exo-3-[4-(4-chloro-phenoxy)-benzenesulfonylamino]-8-oxa-bicyclo[3.2.1]octane-3-carboxylic acid hydroxyamide;

3-endo-3-[4-(4-fluoro-phenoxy)-benzenesulfonylamino]-8-oxa-bicyclo[3.2.1]octane-3-carboxylic acid hydroxyamide; and

3-[4-(4-fluoro-phenoxy)-benzenesulfonylamino]-tetrahydro-furan-3-carboxylic acid hydroxyamide;

and pharmaceutically acceptable salts, solvates and prodrugs of said compounds.

The compounds of formula 1, and the pharmaceutically acceptable salts, solvates and prodrugs thereof, can also be used in combination with signal transduction inhibitors, such as agents that can inhibit EGFR (epidermal growth factor receptor) responses, such as EGFR antibodies, EGF antibodies, and molecules that are EGFR inhibitors; VEGF (vascular endothelial growth factor) inhibitors; and erbB2 receptor inhibitors, such as organic molecules or antibodies that bind to the erbB2 receptor, for example, HERCEPTIN™ (Genentech, Inc. of South San Francisco, California, USA).

EGFR inhibitors are described in, for example in WO 95/19970 (published July 27, 1995), WO 98/14451 (published April 9, 1998), WO 98/02434 (published January 22, 1998), and United States Patent 5,747,498 (issued May 5, 1998). EGFR-inhibiting agents include, but are not limited to, CI-1033 (Pfizer Inc.), the monoclonal antibodies C225 and anti-EGFR 22Mab (ImClone Systems Incorporated of New York, New York, USA), the compounds ZD-1839 (AstraZeneca), BIBX-1382 (Boehringer Ingelheim), MDX-447 (Medarex Inc. of Annandale, New Jersey, USA), and OLX-103 (Merck & Co. of Whitehouse Station, New Jersey, USA), VRCTC-310 (Ventech Research) and EGF fusion toxin (Seragen Inc. of Hopkinton, Massachusettes).

VEGF inhibitors, for example CP-547,632 and AG-13736 (Pfizer, Inc.), SU-5416 and SU-6668 (Sugen Inc. of South San Francisco, California, USA), can also be combined with a compound of formula 1. VEGF inhibitors are described in, for example in WO 99/24440 (published May 20, 1999), PCT International Application PCT/IB99/00797 (filed May 3, 1999), in WO 95/21613 (published August 17, 1995), WO 99/61422 (published December 2, 1999),

United States Patent 5,834,504 (issued November 10, 1998), WO 98/50356 (published November 12, 1998), United States Patent 5,883,113 (issued March 16, 1999), United States Patent 5,886,020 (issued March 23, 1999), United States Patent 5,792,783 (issued August 11, 1998), WO 99/10349 (published March 4, 1999), WO 97/32856 (published September 12, 1997), WO 97/22596 (published June 26, 1997), WO 98/54093 (published December 3, 1998), WO 98/02438 (published January 22, 1998), WO 99/16755 (published April 8, 1999), and WO 98/02437 (published January 22, 1998), all of which are herein incorporated by reference in their entirety. Other examples of some specific VEGF inhibitors are IM862 (Cytran Inc. of Kirkland, Washington, USA); anti-VEGF monoclonal antibody of Genentech, Inc. of South San Francisco, California; and angiozyme, a synthetic ribozyme from Ribozyme (Boulder, Colorado) and Chiron (Emeryville, California).

ErbB2 receptor inhibitors, such as CP-724,714 (Pfizer, Inc.), GW-282974 (Glaxo Wellcome plc), and the monoclonal antibodies AR-209 (Aronex Pharmaceuticals Inc. of The Woodlands, Texas, USA) and 2B-1 (Chiron), may be administered in combination with a compound of formula 1. Such erbB2 inhibitors include those described in WO 98/02434 (published January 22, 1998), WO 99/35146 (published July 15, 1999), WO 99/35132 (published July 15, 1999), WO 98/02437 (published January 22, 1998), WO 97/13760 (published April 17, 1997), WO 95/19970 (published July 27, 1995), United States Patent 5,587,458 (issued December 24, 1996), and United States Patent 5,877,305 (issued March 2, 1999), each of which is herein incorporated by reference in its entirety. ErbB2 receptor inhibitors useful in the present invention are also described in United States Provisional Application No. 60/117,341, filed January 27, 1999, and in United States Provisional Application No. 60/117,346, filed January 27, 1999, both of which are herein incorporated by reference in their entirety.

Other antiproliferative agents that may be used with the compounds of the present invention include inhibitors of HDI (CI-994, Pfizer Inc.), MEK (CI-1040, Pfizer Inc.), the enzyme farnesyl protein transferase and the receptor tyrosine kinase PDGFr, including the compounds disclosed and claimed in the following United States patent applications: 09/221946 (filed December 28, 1998); 09/454058 (filed December 2, 1999); 09/501163 (filed February 9, 2000); 09/539930 (filed March 31, 2000); 09/202796 (filed May 22, 1997); 09/384339 (filed August 26, 1999); and 09/383755 (filed August 26, 1999); and the compounds disclosed and claimed in the following United States provisional patent applications: 60/168207 (filed November 30, 1999); 60/170119 (filed December 10, 1999); 60/177718 (filed January 21, 2000); 60/168217 (filed November 30, 1999), and 60/200834 (filed May 1, 2000). The compounds of the invention may also be used in combination with inhibitors of topoisomerase I, e.g., irinotecan (Camptosar®) and edotecarin. Each of the

foregoing patent applications and provisional patent applications is herein incorporated by reference in their entirety.

A compound of formula 1 may also be used with other agents useful in treating abnormal cell growth or cancer, including, but not limited to, agents capable of enhancing antitumor immune responses, such as CTLA4 (cytotoxic lymphocite antigen 4) antibodies, and other agents capable of blocking CTLA4; and anti-proliferative agents such as other farnesyl protein transferase inhibitors, for example the farnesyl protein transferase inhibitors described in the references cited in the "Background" section, *supra*. Specific CTLA4 antibodies that can be used in the present invention include those described in United States Provisional Application 60/113,647 (filed December 23, 1998) which is herein incorporated by reference in its entirety.

"Abnormal cell growth", as used herein, unless otherwise indicated, refers to cell growth that is independent of normal regulatory mechanisms (e.g., loss of contact inhibition). This includes the abnormal growth of: (1) tumor cells (tumors) that proliferate by expressing a mutated tyrosine kinase or overexpression of a receptor tyrosine kinase; (2) benign and malignant cells of other proliferative diseases in which aberrant tyrosine kinase activation occurs; (4) any tumors that proliferate by receptor tyrosine kinases; (5) any tumors that proliferate by aberrant serine/threonine kinase activation; and (6) benign and malignant cells of other proliferative diseases in which aberrant serine/threonine kinase activation occurs..

The compounds of the present invention are potent inhibitors of the FAK protein tyrosine kinases, and thus are all adapted to therapeutic use as antiproliferative agents (e.g., anticancer), antitumor (e.g., effective against solid tumors), antiangiogenesis (e.g., stop or prevent proliferationation of blood vessels) in mammals, particularly in humans. In particular, the compounds of the present invention are useful in the prevention and treatment of a variety of human hyperproliferative disorders such as malignant and benign tumors of the liver, kidney, bladder, breast, gastric, ovarian, colorectal, prostate, pancreatic, lung, vulval, thyroid, hepatic carcinomas, sarcomas, glioblastomas, head and neck, and other hyperplastic conditions such as benign hyperplasia of the skin (e.g., psoriasis) and benign hyperplasia of the prostate (e.g., BPH). It is, in addition, expected that a compound of the present invention may possess activity against a range of leukemias and lymphoid malignancies.

In one preferred embodiment of the present invention cancer is selected from lung cancer, bone cancer, pancreatic cancer, gastric, skin cancer, cancer of the head or neck, cutaneous or intraocular melanoma, uterine cancer, ovarian cancer, gynecological, rectal cancer, cancer of the anal region, stomach cancer, colon cancer, breast cancer, uterine cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, Hodgkin's Disease, cancer of the esophagus,

cancer of the small intestine, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the adrenal gland, sarcoma of soft tissue, cancer of the urethra, cancer of the penis, squamous cell, prostate cancer, chronic or acute leukemia, lymphocytic lymphomas, cancer of the bladder, cancer of the kidney or ureter, renal cell carcinoma, carcinoma of the renal pelvis, neoplasms of the central nervous system (CNS), primary CNS lymphoma, spinal axis tumors, brain, pituitary adenoma, or a combination of one or more of the foregoing cancers.

In a more preferred embodiment cancer is selected a solid tumor, such as, but not limited to, breast, lung, colon, brain, prostate, stomach, pancreatic, ovarian, skin (melanoma), endocrine, uterine, testicular, and bladder.

The compounds of the present invention may also be useful in the treatment of additional disorders in which aberrant expression ligand/receptor interactions or activation or signalling events related to various protein tyrosine kinases, are involved. Such disorders may include those of neuronal, glial, astrocytal, hypothalamic, and other glandular, macrophagal, epithelial, stromal, and blastocoelic nature in which aberrant function, expression, activation or signalling of the erbB tyrosine kinases are involved. In addition, the compounds of the present invention may have therapeutic utility in inflammatory, angiogenic and immunologic disorders involving both identified and as yet unidentified tyrosine kinases that are inhibited by the compounds of the present invention.

The term "treating", as used herein, unless otherwise indicated, means reversing, alleviating, inhibiting the progress of, or preventing the disorder or condition to which such term applies, or one or more symptoms of such disorder or condition. The term "treatment", as used herein, unless otherwise indicated, refers to the act of treating as "treating" is defined immediately above.

The present invention also provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

The invention further provides a process for the preparation of a pharmaceutical composition of the invention which comprises mixing a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined with a pharmaceutically acceptable adjuvant, diluent or carrier.

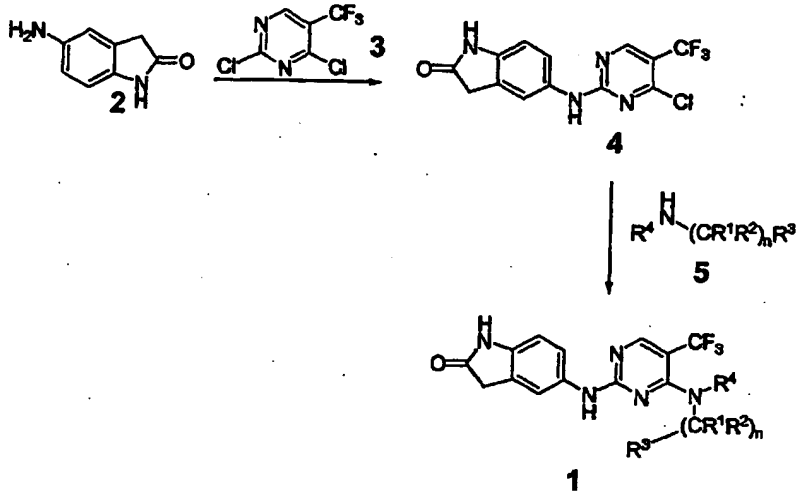
For the above-mentioned therapeutic uses the dosage administered will, of course, vary with the compound employed, the mode of administration, the treatment desired and the disorder indicated. The daily dosage of the compound of formula (I)/salt/solvate (active

ingredient) may be in the range from 1 mg to 1 gram, preferably 1 mg to 250 mg, more preferably 10 mg to 100 mg.

The present invention also encompasses sustained release compositions.

**Detailed Description of the Invention**

The compounds of formula 1 can be prepared using the synthetic route outlined in Scheme 1. The substituents in Scheme 1 have the same meaning as the substituents defined for formula 1.



**Scheme 1**

Compounds of formula 1 can be prepared starting from the 5-amino-oxindole (2) and pyrimidine (3). Combining 3 with an equimolar amount of a Lewis Acid at temperatures ranging from −15 to 45°C for a time period of 10-60 minutes in an inert solvent (or solvent mixture) followed by addition of 2 and a suitable base provides after the period of 1-24 h the intermediate 4-chloropyrimidine (4) in high yields. Examples of inert solvents include but are not limited to THF, 1,4-dioxane, n-BuOH, i-PrOH, dichloromethane and 1,2-dichloroethane. Examples of suitable bases employed may include but are not limited to (i) non-nucleophilic organic bases for example triethylamine or diisopropylethylamine (ii) inorganic bases such as potassium carbonate or cesium carbonate or (iii) resin bound bases such as MP-carbonate.

Examples of Lewis Acids include but are not limited to halide salts of magnesium, copper, zinc, tin or titanium. In the next reaction, intermediate 4 is reacted with an amine of the formula 5 either neat or in the presence of an inert solvent (or solvent mixture) at temperatures ranging from 0 to 150°C to provide the compounds of formula 1. Optionally this reaction can be run in the presence of a suitable base. Examples of suitable solvents for this reaction include but are not limited to THF, 1,4-dioxane, DMF, N-methyl-pyrrolidinone, EtOH, n-BuOH, i-PrOH,

dichloromethane, 1,2-dichloroethane, DMSO or acetonitrile. Suitable bases are as outlined above.

Compounds of the present invention may be synthetically transformed into other compounds of the invention by techniques known to those skilled in the art. Simply for illustrative purposes and without limitation, such methods include:

a) removal of a protecting group by methods outlined in T. W. Greene and P.G.M. Wuts, "Protective Groups in Organic Synthesis", Second Edition, John Wiley and Sons, New York, 1991; e.g., emoval of a BOC protecting group with an acid source such as HCl or trifluoroacetic acid.

b) displacement of a leaving group (halide, mesylate, tosylate, etc) with functional groups such as but not limited to a primary or secondary amine, thiol or alcohol to form a secondary or tertiary amine, thioether or ether, respectively.

c) treatment of phenyl (or substituted phenyl) carbamates with primary of secondary amines to form the corresponding ureas as in Thavonekham, B et. al. Synthesis (1997), 10, p1189;

d) reduction of propargyl or homopropargyl alcohols or N-BOC protected primary amines to the corresponding E-allylic or E-homoallylic derivatives by treatment with sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al) as in Denmark, S. E.; Jones, T. K. J. Org. Chem. (1982) 47, 4595-4597 or van Benthem, R. A. T. M.; Michels, J. J.; Speckamp, W. N. Synlett (1994), 368-370;

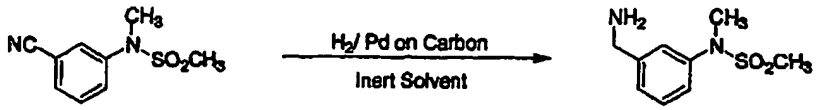
e) reduction of alkynes to the corresponding Z-alkene derivatives by treatment hydrogen gas and a Pd catalyst as in Tomassy, B. et. al. Synth. Commun. (1998), 28, p1201

f) treatment of primary and secondary amines with an isocyanate, acid chloride (or other activated carboxylic acid derivative), alkyl/aryl chloroformate or sulfonyl chloride to provide the corresponding urea, amide, carbamate or sulfonamide;

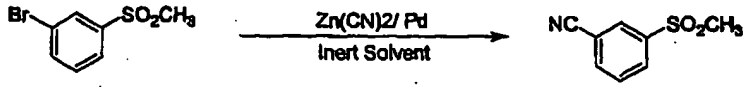
g) reductive amination of a primary or secondary amine using an aldehyde or ketone and an appropriate reducing reagent.

h) treatment of alcohols with an isocyanate, acid chloride (or other activated carboxylic acid derivative), alkyl/aryl chloroformate or sulfonyl chloride to provide the corresponding carbamate, ester, carbonate or sulfonic acid ester.

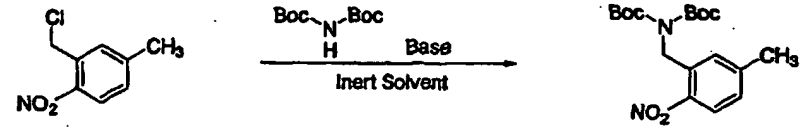
Amines of the formula 5 may be purchased and used directly or alternatively be prepared by one skilled in the art using ordinary chemical transformations. For example; arylalkylamines or heteroarylalkylamines may be prepared from the corresponding nitrile by catalytic hydrogenation using catalysts such as Pd/C or Raney Nickel or by lithium aluminum hydride reduction, (see Rylander, Catalytic Hydrogenation in Organic Synthesis, Academic Press, 1979).



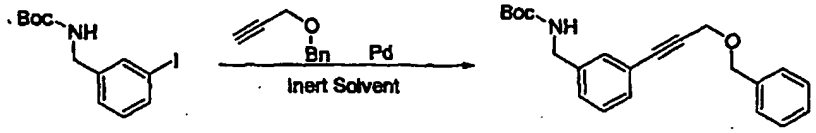

The nitrile starting materials can be either purchased or prepared from the corresponding aryl/heteroaryl bromide, iodide or triflate and Zn(CN)2 using Pd coupling conditions found in Tschaen, D. M., et. al Synthetic Communications (1994), 24, 6, pp 887-890.




Alternatively, benzylamines or heteroarylmethylamines can be prepared by reacting the appropriate arylalkyl or heteroarylalkyl halide and the potassium salt of $(BOC)_2NH$ (reference) and subsequent removal of the BOC groups with acid.



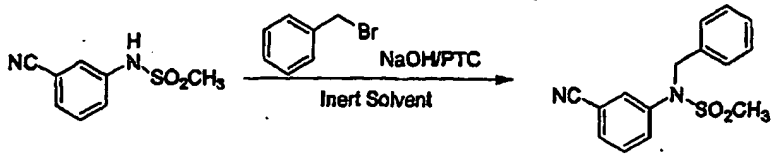

Amines, protected forms of amines, precursors to amines and precursors to the protected forms of amines of formula 5 can be prepared by combining the appropriate alkyne, or alkenyl stannane, alkenyl borane, alkenyl boronic acid, boronic ester with the appropriate aryl or heteroaryl bromide, iodide or triflate using Pd coupling conditions as found in Tsuji, J.; Palladium Reagents and Catalysis, John Wiley and Sons 1999 and references cited therein.



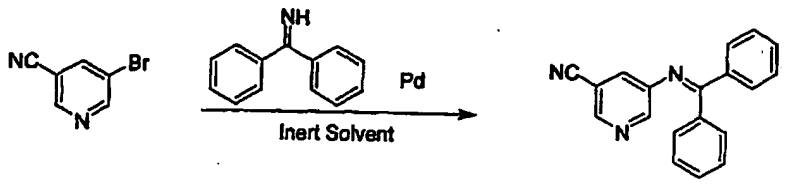

Appropriately protected amines of formula 5 may be converted to different amines of formula 5 according to methods familiar to those skilled in the art for exampleas but limited to:

(a) oxidation of a thioether to a sulfoxide or sulfone.


(b) N-alkylation of a sulfanilide can be achieved under phase transfer using conditions described by Brehme, R. "Synthesis", (1976), pp113-114.



As understood by those skilled in the art, the chemical transformation to convert an aryl halide or triflate or heteroaryl halide or triflate to an aromatic or heteroaromatic amine may be carried out using conditions currently outlined in the literature, see Hartwig, J. F.: "Angew. Chem. Int. Ed." (1998), 37, pp. 2046-2067, Wolfe, J. P.; Wagaw, S.; Marcoux, J. F.; Buchwald, S.L.; "Acc. Chem. Res.", (1998), 31, pp 805-818, Wolfe, J. P.; Buchwald, S.L.; "J. Org. Chem.", (2000), 65, pp 1144-1157, Mucl, A. R.; Buchwald, S. L.; "Topics in Current Chemistry" (2002), pp131-209 and references cited therein. Further, as understood by those skilled in the art, these same aryl or heteroaryl amination chemical transformations may alternatively be carried out on nitrile (or primary amide) precursors which provide amines of the formula **5** after nitrile (or amide) reduction. Protected amines of formula **5** may be further converted to different amines of formula **5** according to methods familiar to those skilled in the art.




The *in vitro* activity of the compounds of formula **1** may be determined by the following procedure. More particularly, the following assay provides a method to determine whether compounds of the formula **1** inhibit the tyrosine kinase activity of the catalytic construct FAK(410-689). The assay is an ELISA-based format, measuring the inhibition of poly-glu-tyr phosphorylation by FAK(410-689).

The assay protocol has three parts:

I. Purification and cleavage of His-FAK(410-689)

II. FAK410-689 (a.k.a. FAKcd) Activation

III. FAKcd Kinase ELISA

Materials:

-Ni-NTA agarose (Qiagen)

-XK-16 column (Amersham-Pharmacia)

-300 mM Imidizole

-Superdex 200 HiLoad 16/60 prep grade column (Amersham Biotech.)

-Antibody: Anti-Phosphotyrosine HRP-Conjugated Py20 (Transduction labs).

-FAKcd: Purified and activated in house

-TMB Microwell Peroxidase Substrate (Oncogene Research Products #CL07)

-BSA: Sigma #A3294

-Tween-20: Sigma #P1379

-DMSO: Sigma #D-5879

-D-PBS: Gibco #14190-037.

Reagents for Purification:

-Buffer A: 50mM HEPES pH 7.0,
500mM NaCl,
0.1mM TCEP
CompleteTM protease inhibitor cocktail tablets (Roche)
-Buffer B: 25mM HEPES pH 7.0,
400mM NaCl
0.1mM TCEP.
-Buffer C: 10mM HEPES pH 7.5,
200mM Ammonium Sulfate
0.1mM TCEP.

**Reagents for Activation**

-FAK(410-689): 3 tubes of frozen aliquots at 150ul/tube for a total of 450ul at 1.48 mg/ml (660ug)
-His-Src(249-524): ~0.74 mg/ml stock in 10mM HEPES, 200mM (NH4)2SO4
-Src reaction buffer (Upstate Biotech):
100 mM Tris-HCl pH7.2,
125mM MgCl2,
25 mM MnCl2,
2mM EDTA,
250 uM Na3VO4,
2 mM DTT
-Mn2+/ATP cocktail (Upstate Biotech)
75mM MnCl2
500 uM ATP
20mM MOPS pH 7.2
1mM Na3VO4
25mM □-glycerol phosphate
5mM EGTA
1mM DTT
-ATP: 150mM stock
-$MgCl_2$: 1 M Stock
-DTT: 1M stock

**Reagents for FAKcd Kinase ELISA**

-Phosphorylation Buffer:

50mM HEPES, pH 7.5,
125mM NaCl,
48mM MgCl2

-Wash Buffer: TBS + 0.1% Tween-20.

-Blocking Buffer:
Tris Buffer Saline,
3% BSA,
0.05% Tween-20, filtered.

-Plate Coating Buffer:
50mg/ml Poly-Glu-Tyr (Sigma #P0275) in Phosphate buffer Saline (DPBS).

-ATP: 0.1M ATP in H2O or HEPES, pH7.
Note: ATP Assay Buffer:
Make up as 75 uM ATP in PBS, so that 80 ul in
120 ul reaction volume=50uM final ATP concentration.

**I. Purification of His-FAKcd(410-689)**

1. Resuspend 130 g baculovirus cell paste containing the over expressed His-FAKcd410-689 recombinant protein in 3 volumes (400ml) of Buffer A,
2. Lyse cells with one pass on a microfluidizer
3. Remove cell debris by centrifugation at 4OC for 35 minutes at 14,000 rpm in a Sorval SLA-1500 rotor.
4. Transfer the supernatant to a clean tube and add 6.0 ml of Ni-NTA agarose (Qiagen)
5. Incubate the suspension with gentle rocking at 4OC for 1 hour
6. Centrifuge suspension at 700 x g in a swinging bucket rotor.
7. Discard the supernatant and resuspend the agarose beads in 20.0 ml of Buffer A
8. Transfer the beads to an XK-16 column (Amersham-Pharmacia) connected to a FPLCTM.
9. Wash the agarose-beads with 5 column volumes of Buffer A and elute off the column with a step gradient of Buffer A containing 300mM Imidizole.
10. Perform a buffer exchange of the eluted fractions into Buffer B
11. Following buffer exchange, pool the fractions and add thrombin at a 1:300 (w/w) ratio and incubated overnight at 13°C to remove the N-terminal His-tag (His-FAK410-698 → FAK410-689 (a.k.a. FAKcd)).
12. Add the reaction mixture back onto the Ni-NTA column equilibrated with Buffer A and collect the flow-through.

13. Concentrate the flow-through down to 1.7 ml and load directly onto a Superdex 200 HiLoad 16/60 prep grade column equilibrated with Buffer C. The desired protein elutes between 85 - 95 ml.

14. Aliquot the FAKcd protein and store frozen at –80°C

**II. FAK activation**

1. To 450ul of FAK(410-689) at 1.48 mg/ml (660ug) add the following:
   30ul of 0.037 mg/ml (1uM) His-Src(249-524)
   30ul of 7.5 mM ATP
   12ul of 20 mM MgCl2
   10ul Mn2+/ATP cocktail (UpState Biotech.)
   4ul of 6.7mM DTT
   60ul Src Reaction Buffer (UpState Biotech.)
2. Incubate Reaction for at least 3 hours at room temperature

At time $t_0$, almost all of the FAK(410-689) is singly phosphorylated. The second phosphorylation is slow. At $t_{120}$ (t = 120 minutes), add 10ul of 150 mM ATP.

$T_0$ = (Start) 90% singly phosphorylated FAK(410-689) (1 PO4)

$T_{43}$ = (43 min) 65% singly phosphorylated (1 PO4), 35% doubly phosphorylated (2 PO4)

$T_{90}$ = (90 min) 45% 1 PO4, 55% 2 PO4

$T_{150}$ = 15% 1 PO4, 85% 2 PO4

$T_{210}$ = <10% 1 PO4, >90% 2 PO4 desalted sample

3. Add 180 ul aliquots of the desalted material to NiNTA spin column and incubate on spin column

4. Spin at 10k rpm (microfuge), for 5 min to isolate and collect flow through (Activated FAK(410-689)) and remove His-Src (captured on column)

**III. FAKcd Kinase ELISA**

1. Coat 96-well Nunc MaxiSorp plates with poly-glu-tyr (pGT) at 10 ug/well: Prepare 10 ug/ml of pGT in PBS and aliquot 100 ul/well. Incubate the plates at 37°C overnight, aspirate the supernatant, wash the plates 3 times with Wash Buffer, and flick to dry before storing at 4°C.

2. Prepare compound stock solutions of 2.5 mM in 100% DMSO. The stocks are subsequently diluted to 60X of the final concentration in 100% DMSO, and diluted 1:5 in Kinase Phosphorylation Buffer.

3. Prepare a 75 uM working ATP solution in Kinase phosphorylation buffer. Add 80 ul to each well for a final ATP concentration of 50 uM.

4. Transfer 10 ul of the diluted compounds (0.5log serial dilutions) to each well of the pGT assay plate, running each compound in triplicates on the same plate.

5. Dilute on ice, FAKcd protein to 1:1000 in Kinase Phosphorylation Buffer. Dispense 30 ul per well.

6. Note: Linearity and the appropriate dilution must be pre-determined for each batch of protein. .The enzyme concentration selected should be such that quantitation of the assay signal will be approximately 0.8-1.0 at OD450, and in the linear range of the reaction rate.

7. Prepare both a No ATP control (noise) and a No Compound Control (Signal):

8. (Noise) One blank row of wells receives 10 ul of 1:5 diluted compounds in DMSO, 80ul of Phosphorylation buffer (minus ATP), and 30 ul FAKcd solution.

9. (Signal) Control wells receive 10 ul of 1:5 diluted DMSO (minus Compound) in Kinase phosphorylation buffer, 80 ul of 75 uM ATP, and 30 ul of 1:1000 FAKcd enzyme.

10. Incubate reaction at room temperature for 15 minutes with gentle shaking on a plate shaker.

11. Terminate the reaction by aspirating off the reaction mixture and washing 3 times with wash buffer.

12. Dilute phospho-tyrosine HRP-conjugated (pY20HRP) antibody to 0.250ug/ml (1:1000 of Stock) in blocking buffer. Dispense 100 ul per well, and incubate with shaking for 30min. at R.T.

13. Aspirate the supernatant and wash the plate 3 times with wash buffer.

14. Add 100 ul per well of room temperature TMB solution to initiate color development. Color development is terminated after approximately 15-30 sec. by the addition of 100ul of 0.09M H2SO4 per well.

15. The signal is quantitated by measurement of absorbance at 450nm on the BioRad microplate reader or a microplate reader capable of reading at OD450.

16. Inhibition of tyrosine kinase activity would result in a reduced absorbance signal. The signal is typically 0.8-1.0 OD units. The values are reported as $IC_{50s}$, uM concentration.

**FAK Inducible cell-based ELISA: Final Protocol**

**Materials:**

Reacti-Bind Goat Anti-Rabbit Plates 96-well (Pierce Product#15135ZZ @115.00 USD)

FAKpY397 rabbit polyclonal antibody (Biosource #44624 @315.00 USD)

ChromePure Rabbit IgG, whole molecule (Jackson Laboratories #001-000-003 @60/25mg USD)

UBI αFAK clone 2A7 mouse monoclonal antibody (Upstate#05-182 @ 289.00 USD)

Peroxidase-conjugated AffiniPure Goat Anti-Mouse IgG (Jackson Labs #115-035-146 @95/1.5ml USD)

SuperBlock TBS (Pierce Product#37535ZZ @99 USD)

Bovine Serum Albumin (Sigma #A-9647 @117.95/100 g USD)

TMB Peroxidase substrate (Oncogene Research Products #CL07-100ml @40.00 USD)

Na3VO4 Sodium Orthovanadate (Sigma #S6508 @43.95/50g USD)

MTT substrate (Sigma # M-2128 @25.95/500mg USD)

Growth Media: DMEM+10%FBS, P/S, Glu, 750 ug/ml Zeocin and 50 ug/ml Hygromycin (Zeocin InVitrogen #R250-05 @ 725 USD and Hygromycon InVitrogen #R220-05 @ 150 USD)

Mifepristone InVitrogen # H110-01 @ 125 USD

CompleteTM EDTA-free Protease Inhibitor pellet Boehringer Mannheim #1873580

FAK cell-based Protocol for selectivity of kinase-dependent phosphoFAKY397

**Procedure:**

An inducible FAK cell-based assay in ELISA format for the screening of chemical matter to identify tyrosine kinase specific inhibitors was developed. The cell-based assay exploits the mechanism of the GeneSwitchTM system (InVitrogen) to exogenously control the expression and phosphorylation of FAK and the kinase-dependent autophosphorylation site at residue Y397.

Inhibition of the kinase-dependent autophosphorylation at Y397 results in a reduced absorbance signal at OD450. The signal is typically 0.9 to 1.5 OD450 units with the noise falling in the range of 0.08 to 0.1 OD450 units. The values are reported as IC50s, uM concentration.

On day 1, grow A431•FAKwt in T175 flasks. On the day prior to running the FAK cell-assay, seed A431•FAKwt cells in growth media on 96-well U-bottom plates. Allow cells to sit at 37oC, 5% CO2 for 6 to 8 hours prior to FAK induction. Prepare Mifepristone stock solution of 10 uM in 100 % Ethanol. The stock solution is subsequently diluted to 10 X of the final concentration in Growth Media. Transfer 10 ul of this dilution (final concentration of 0.1 nM Mifepristone) into each well. Allow cells to sit at 37oC, 5% CO2 overnight (12 to 16 hours). Also, prepare control wells without Mifepristone induction of FAK expression and phosphorylation.

On day 2, coat Goat Anti-Rabbit plate(s) with 3.5 ug/ml of phosphospecific FAKpY397 polyclonal antibody prepared in SuperBlock TBS buffer, and allow plate(s) to shake on a plate shaker at room temperature for 2 hours. Optionally, control wells may be coated with 3.5 ug/ml of control Capture antibody (Whole Rabbit IgG molecules) prepared in SuperBlock TBS. Wash

off excess FAKpY397 antibody 3 times using buffer. Block Anti-FAKpY397 coated plate(s) with 200 ul per well of 3%BSA/0.5%Tween Blocking buffer for 1 hour at room temperature on the plate shaker. While the plate(s) are blocking, prepare compound stock solutions of 5 mM in 100 % DMSO. The stock solutions are subsequently serially diluted to 100X of the final concentration in 100% DMSO. Make a 1:10 dilution using the 100X solution into growth media and transfer 10 ul of the appropriate compound dilutions to each well containing either the FAK induced or uninduced control A431 cells for 30 minutes at 37oC, 5% CO2. Prepare RIPA lysis buffer (50 mM Tris-HCl, pH7.4, 1% NP-40, 0.25% Na-deoxycholate, 150 mM NaCl, 1 mM EDTA, 1 mM Na3VO4, 1 mM NaF, and one CompleteTM EDTA-free protease inhibitor pellet per 50 ml solution). At the end of 30 minutes compound treatment, wash off compound 3 times using TBS-T wash buffer. Lyse cells with 100 ul/well of RIPA buffer.

To the coated plate, remove blocking buffer and wash 3 times using TBS-T wash buffer. Using a 96-well automated microdispenser, transfer 100 ul of whole cell-lysate (from step 6) to the Goat Anti-Rabbit FAKpY397 coated plate(s) to capture phosphoFAKY397 proteins. Shake at room temperature for 2 hours. Wash off unbound proteins 3 times using TBS-T wash buffer. Prepare 0.5 ug/ml (1:2000 dilution) of UBI αFAK detection antibody in 3%BSA/0.5% Tween blocking buffer. Dispense 100 ul of UBI αFAK solution per well and shake for 30 minutes at room temperature. Wash off excess UBI αFAK antibody 3 times using TBS-T wash buffer. Prepare 0.08 ug/ml (1:5000 dilution) of secondary Anti-Mouse Peroxidase (Anti-2MHRP) conjugated antibody. Dispense 100 ul per well of the Anti-2MHRP solution and shake for 30 minutes at room temperature. Wash off excess Anti-2MHRP antibody 3 times using TBS-T wash buffer. Add 100 ul per well of room temperature TMB substrate solution to allow for color development. Terminate the TMB reaction with 100 ul per well of TMB stop solution (0.09M H2SO4) and quantitate the signal by measurement of absorbance at 450 nm on the BioRad microplate reader.

**Additional FAK cell assays are hereby incorporated by reference from Pfizer Attorney Docket No. PC11699 *entitled* "INDUCIBLE FOCAL ADHESION KINASE CELL ASSAY".**

In a preferred embodiment, the compounds of the present invention have an in vivo activity as determined by a kinase assay, e.g., such as that described herein, of less than 100 nM. Preferably, the compounds have an $IC_{50}$ of less than 25 nM in the kinase assay, and more preferably less than 10 nM. In a further preferred embodiment, the compounds exhibit an $IC_{50}$ in a FAK cell based assay, e.g., such as that described herein, of less than 1 □M, more preferably less than 100 nM, and most preferably less than 25 nM.

Administration of the compounds of the present invention (hereinafter the "active compound(s)") can be effected by any method that enables delivery of the compounds to the

site of action. These methods include oral routes, intraduodenal routes, parenteral injection (including intravenous, subcutaneous, intramuscular, intravascular or infusion), topical, and rectal administration.

The amount of the active compound administered will be dependent on the subject being treated, the severity of the disorder or condition, the rate of administration, the disposition of the compound and the discretion of the prescribing physician. However, an effective dosage is in the range of about 0.001 to about 100 mg per kg body weight per day, preferably about 1 to about 35 mg/kg/day, in single or divided doses. For a 70 kg human, this would amount to about 0.05 to about 7 g/day, preferably about 0.2 to about 2.5 g/day. In some instances, dosage levels below the lower limit of the aforesaid range may be more than adequate, while in other cases still larger doses may be employed without causing any harmful side effect, provided that such larger doses are first divided into several small doses for administration throughout the day.

The active compound may be applied as a sole therapy or may involve one or more other anti-tumour substances, for example those selected from, for example, mitotic inhibitors, for example vinblastine; alkylating agents, for example cis-platin, carboplatin and cyclophosphamide; anti-metabolites, for example 5-fluorouracil, cytosine arabinoside and hydroxyurea, or, for example, one of the preferred anti-metabolites disclosed in European Patent Application No. 239362 such as N-(5-[N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-methylamino]-2-thenoyl)-L-glutamic acid; growth factor inhibitors; cell cycle inhibitors; intercalating antibiotics, for example adriamycin and bleomycin; enzymes, for example interferon; and anti-hormones, for example anti-estrogens such as Nolvadex□ (tamoxifen) or, for example anti-androgens such as Casodex□ (4'-cyano-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methyl-3'-(trifluoromethyl)propionanilide). Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate dosing of the individual components of the treatment.

The pharmaceutical composition may, for example, be in a form suitable for oral administration as a tablet, capsule, pill, powder, sustained release formulations, solution, suspension, for parenteral injection as a sterile solution, suspension or emulsion, for topical administration as an ointment or cream or for rectal administration as a suppository. The pharmaceutical composition may be in unit dosage forms suitable for single administration of precise dosages. The pharmaceutical composition will include a conventional pharmaceutical carrier or excipient and a compound according to the invention as an active ingredient. In addition, it may include other medicinal or pharmaceutical agents, carriers, adjuvants, etc.

Exemplary parenteral administration forms include solutions or suspensions of active compounds in sterile aqueous solutions, for example, aqueous propylene glycol or dextrose solutions. Such dosage forms can be suitably buffered, if desired.

Suitable pharmaceutical carriers include inert diluents or fillers, water and various organic solvents. The pharmaceutical compositions may, if desired, contain additional ingredients such as flavorings, binders, excipients and the like. Thus for oral administration, tablets containing various excipients, such as citric acid may be employed together with various disintegrants such as starch, alginic acid and certain complex silicates and with binding agents such as sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often useful for tableting purposes. Solid compositions of a similar type may also be employed in soft and hard filled gelatin capsules. Preferred materials, therefor, include lactose or milk sugar and high molecular weight polyethylene glycols. When aqueous suspensions or elixirs are desired for oral administration the active compound therein may be combined with various sweetening or flavoring agents, coloring matters or dyes and, if desired, emulsifying agents or suspending agents, together with diluents such as water, ethanol, propylene glycol, glycerin, or combinations thereof.

Methods of preparing various pharmaceutical compositions with a specific amount of active compound are known, or will be apparent, to those skilled in this art. For examples, see Remington's Pharmaceutical Sciences, Mack Publishing Company, Easter, Pa., 15th Edition (1975).

The examples and preparations provided below further illustrate and exemplify the compounds of the present invention and methods of preparing such compounds. It is to be understood that the scope of the present invention is not limited in any way by the scope of the following examples and preparations. In the following examples molecules with a single chiral center, unless otherwise noted, exist as a racemic mixture. Those molecules with two or more chiral centers, unless otherwise noted, exist as a racemic mixture of diastereomers. Single enantiomers/diastereomers may be obtained by methods known to those skilled in the art.

Where HPLC chromatography is referred to in the preparations and examples below, the general conditions used, unless otherwise indicated, are as follows. The column used is a ZORBAX□ RXC18 column (manufactured by Hewlett Packard) of 150 mm distance and 4.6 mm interior diameter. The samples are run on a Hewlett Packard-1100 system. A gradient solvent method is used running 100 percent ammonium acetate / acetic acid buffer (0.2 M) to 100 percent acetonitrile over 10 minutes. The system then proceeds on a wash cycle with 100 percent acetonitrile for 1.5 minutes and then 100 percent buffer solution for 3 minutes. The flow rate over this period is a constant 3 ml / minute.

In the following examples and preparations, "Et" means ethyl, "Ac" means acetyl, "Me" means methyl, and "Bu" means butyl.

Examples

General Methods:

Preparation of 5-nitro-oxindole:

To a solution of oxindole (26 g) in 100 mL of concentrated sulfuric acid at –15oC was added fuming nitric acid (8.4 mL) dropwise. Careful attention was paid to maintain the reaction temperature at –15oC. After the addition was complete, the reaction was stirred for 30 minutes and then poured into ice water. A yellow precipitate was formed which was isolated by filtration to provide 34 grams (98%) of 5-nitro oxindole.

Preparation of 5-amino-oxindole (2):

To a solution of 5-nitro-oxindole (25 g) in 120 mL of dimethylacetamide in a Parr bottle was added 10% Pd/C (0.5 g). The mixture was hydrogenated (40 psi H2) for 16 h. The catalyst was removed by filtration and the filtrate was diluted with ether (2L) to provide 5-amino-oxindole (10.5 g; 50%).

Preparation of 2,4-dichloro-5-trifluoromethylpyrimidine (3):

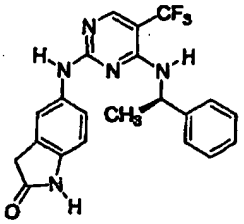
5-Trifluoromethyluracil (250g, 1.39 mol) and phosphorous oxychloride (655 mL, 6.94 mol, 5 equiv) were charged to a 3L 4-neck flask equipped with overhead stirrer, a reflux condenser, an addition funnel and an internal theromocouple. The contents were maintained under a nitrogen atmosphere as concentrated phosphoric acid (85 wt%, 9.5 mL, 0.1 equiv) was added in one portion to the slurry, resulting in a moderate exotherm. Diisopropylethylamine (245 mL, 1.39 mol, 1 equiv) was then added dropwise over 15 min at such a rate that the internal temperature of the reaction reached 85–90 °C by the end of the addition. By the end of the amine addition the reaction mixture was a homogenous light-orange solution. Heating was initiated and the orange solution was maintained at 100 °C for 20h, at which time HPLC analysis of the reaction mixture indicated that the starting material was consumed. External heating was removed and the contents of the flask were cooled to 40 °C and then added dropwise to a cooled mixture of 3N HCl (5 L, 10 equiv) and diethyl ether (2L) keeping the temperature of the quench pot between 10 and 15 °C. The layers were separated, and the aqueous layer was extracted once with ether (1L). The combined organic layers were combined, washed with water until the washes were neutral (5 × 1.5L washes), dried with $MgSO_4$ and concentrated to provide 288g (95% yield) of a light yellow-orange oil of 96% purity (HPLC). This material can be further purified by distillation (bp 109 °C at 79 mmHg).

Preparation of 5-(4-Chloro-5-trifluoromethyl-pyrimidin-2-ylamino)-1,3-dihydro-indol-2-one (4):

To a solution of 5-trifluoromethyl-2,4-dichloropyrimidine (214.8 g; 0.921 mol) in 1:1 DCE/tBuOH (1.240 L) was added Zinc chloride 1M solution in ether (1 eq; 0.921 L). After 0.5 hour, 5-amino-oxindole (124 g; 0.837 mol) was added followed by triethylamine (129.4 ml; 0.921 mol) keeping temperature at 25° C. The reaction was allowed to stir at room temperature overnight, then was concentrated and the product triturated from methanol as a yellow solid (224.3 g; 82%). $^1$H NMR (DMSO-$d_6$, 400 MHz) □ 3.29 (s, 2H), 6.76 (d, J = 7.9 Hz, 2H), 7.39 (d, J = 8.3 Hz), 7.51 (br s, 1H), 8.71 (s, 1H), 10.33 (s, 1H), 10.49 (s, 1H). $^{13}$C NMR (DMSO-$d_6$, 100 MHz) □ 177.0, 161.3, 158.7 (br), 140.7, 132.8, 126.9, 123.7 (q, J = 268 Hz), 121.0, 118.7, 111.2 (q, J = 32 Hz), 109.6, 36.7; HPLC ret. time: 5.759 min. LRMS (M+) 329.1, 331.1.

Example 1

5-[4-(R-1-Phenyl-ethylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one



To a solution of 1:1 DCE/t-BuOH alcohol (1:1 ratio, 4 mL) and 5-(4-Chloro-5-trifluoromethyl-pyrimdin-2-ylamino)-1,3-dihydro-indol-2-one (0.15 g; 0.456 mmole) was added (R)(+) alpha phenethyl amine (0.071 mL; 0.547 mmole) and diisopropyl ethyl amine (0.081 mL, 0.456 mmole). The resultant solution was stirred under nitrogen and heated to 80°C for 16 hours. The reaction was cooled to room temperature, diluted with ~10 mL of a 1:1 mixture of dichloromethane and methanol followed by the addition of 0.5 g of MP-carbonate. The resultant mixture was stirred, filtered, concentrated and purified by silica gel chromatography (97:2.8:0.3 ratio of chloroform/methanol/concentrated ammonium hydroxide). The desired title compounds was obtained as a white solid (0.021 g; 11%). HPLC ret. time: 6.46 min. LRMS (M+) 413.4

The following compounds of the invention were prepared by heating chloropyrimidine (4) with an appropriate amine as in Example 1. Amines used in these reactions were either obtained commercially and used as received or alternatively they were prepared by common synthetic methods for amines known to those skilled in the art. Unless otherwise noted, compounds having chiral centers were prepared as racemic mixtures.

Table 1. Compounds Prepared by the Method of Example 1:

| Compound Name | HPLC Retention Time (min.) | MS Data (M+H) |
|---|---|---|
| N-(1-Methyl-1-phenyl-ethyl)-3-{[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-methyl}-benzenesulfonamide | 6.46 | 597.5 |
| 3-{[2-(2-Oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-methyl}-benzenesulfonamide | 4.87 | 479.1 |
| 5-{4-[3-(Trifluoro-methanesulfonyl)-benzylamino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one | 6.35 | 532.1 |
| 5-{4-[(Piperidin-3-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one | 3.74 | 407.3 |
| 5-{4-[(1-Methanesulfonyl-piperidin-3-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one | 5.21 | 485.2 |
| N-(3-{[2-(2-Oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-methyl}-phenyl)-methanesulfonamide | 5.22 | 493.3 |
| 3-Oxo-3-{3-{[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-methyl}-piperidin-1-yl)-propionitrile | 4.92 | 474.3 |
| 5-{4-[3-(1,1-Dioxo-1$N^6$-isothiazolidin-2-yl)-propylamino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one | 4.89 | 471.1 |
| 5-[4-(2-Methyl-butylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one | 6.53 | 380.3 |
| 5-{4-[(1-Methanesulfonyl-piperidin-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino)-1,3-dihydro-indol-2-one | 5.17 | 485.3 |
| N-{2-[2-(2-Oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-ethyl}-methanesulfonamide | 4.38 | 431.2 |
| N-{4-[2-(2-Oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-butyl}-methanesulfonamide | 4.78 | 459.3 |
| 5-{4-[(1-Methanesulfonyl-piperidin-4-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one | 5.22 | 485.3 |
| N-Methyl-N-{2-[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-ethyl}-methanesulfonamide | 4.81 | 445.1 |
| Methanesulfonic acid 3-{[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-methyl}-phenyl ester | 5.67 | 494.1 |
| N-{3-[2-(2-Oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-propyl}-methanesulfonamide | 4.58 | 445.1 |
| 5-{4-[(4-Methanesulfonyl-morpholin-2-ylmethyl)- | 4.87 | 487.2 |

| Compound Name | HPLC Retention Time (min.) | MS Data (M+H) |
|---|---|---|
| amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one | | |
| N-(4-Fluoro-3-{[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-methyl}-phenyl)-methanesulfonamide | 5.29 | 511.1 |
| 5-{4-[(5-Oxo-morpholin-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one | 4.12 | 423.3 |
| N-(4-Methoxy-3-{[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-methyl}-phenyl)-methanesulfonamide | 5.38 | 523.2 |
| N-(4-Methyl-3-{[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-methyl}-phenyl)-methanesulfonamide | 5.30 | 507.2 |
| 5-[4-(3-Methanesulfonylmethyl-benzylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one | 5.14 | 492.2 |
| 5-{4-[(4-Trifluoroacetyl-morpholin-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one | 5.64 | 505.1 |
| 5-{4-[(1-Methanesulfonyl-azetidin-3-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one | 4.76 | 457.2 |
| N-Methyl-N-(4-methyl-3-{[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-methyl}-phenyl)-methanesulfonamide | 6.66 | 521.3 |
| 5-{4-[(1-Methanesulfonyl-pyrrolidin-3-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one | 4.97 | 471.2 |
| N-Methyl-N-{3-[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-propyl}-methanesulfonamide | 5.02 | 459.2 |
| 5-{4-[2-(1-Methanesulfonyl-piperidin-2-yl)-ethylamino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one | 5.71 | 499.4 |
| 5-{4-[(4-Methanesulfonyl-pyridin-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one | 4.68 | 479.1 |
| {2,2-Dimethyl-3-[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-propyl}-carbamic acid tert-butyl ester | 7.01 | 495.0 |
| 5-[4-(3-Isopropoxy-propylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one | 6.27 | 410.4 |
| 5-{4-[(1-Methyl-piperidin-3-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one | 3.71 | 421.0 |
| 5-{4-[(Tetrahydro-pyran-4-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2- | 5.16 | 408.3 |

| Compound Name | HPLC Retention Time (min.) | MS Data (M+H) |
|---|---|---|
| one | | |
| 5-[4-(2-Ethyl-butylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one | 6.95 | 394.3 |
| 5-{4-[(Tetrahydro-furan-2R-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one | 5.30 | 394.3 |
| 5-{4-[(Tetrahydro-furan-2S-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one | 5.30 | 394.3 |
| 5-{4-[(5-Methyl-furan-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one | 5.98 | 404.2 |
| 5-{4-[(1-Methanesulfonyl-pyrrolidin-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one | 5.08 | 471.3 |
| 5-{4-[(Adamantan-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one | 7.89 | 458.3 |
| 5-{4-[(Adamantan-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one | 5.20 | 473.3 |
| 5-[4-(2-Methoxy-2-methyl-propylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one | 5.87 | 396.3 |
| 5-{4-[(*endo*-Bicyclo[2.2.1]hept-5-en-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one | 6.74 | 416.3 |
| (3-{[2-(2-Oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-methyl}-benzyl)-phosphonic acid dimethyl ester | 5.03 | 522.2 |
| 5-[4-(3-Methyl-butylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one | 6.87 | 380.2 |
| 5-{4-[(2-Hydroxy-cyclohexylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one | 6.66 | 422.2 |
| N-(4-Methoxy-3-{[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-methyl}-phenyl)-N-methyl-methanesulfonamide | 5.69 | 537.2 |
| 5-{4-[(4-Ethanesulfonyl-morpholin-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one | 5.11 | 501.3 |
| 5-(4-{[4-(Propane-2-sulfonyl)-morpholin-2-ylmethyl]-amino}-5-trifluoromethyl-pyrimidin-2-ylamino)-1,3-dihydro-indol-2-one | 5.35 | 515.2 |
| 5-{4-[(4-Acetyl-morpholin-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one | 4.43 | 451.2 |
| 5-{4-[(4-Propionyl-morpholin-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol- | 4.74 | 465.2 |

| Compound Name | HPLC Retention Time (min.) | MS Data (M+H) |
|---|---|---|
| 2-one | | |
| 5-(4-{[4-(2,2-Dimethyl-propionyl)-morpholin-2-ylmethyl]-amino}-5-trifluoromethyl-pyrimidin-2-ylamino)-1,3-dihydro-indol-2-one | 5.43 | 493.2 |
| 2-{[2-(2-Oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-methyl}-morpholine-4-carboxylic acid methyl ester | 5.04 | 467.2 |
| 5-{4-[(4-Methoxyacetyl-morpholin-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one | 4.44 | 481.2 |
| 5-[4-(3-Ethanesulfonyl-benzylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one | 5.36 | 492.3 |
| 5-{4-[(4-Methanesulfonyl-morpholin-2R-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one | 4.84 | 487.3 |
| 5-{4-[(4-Methanesulfonyl-morpholin-2S-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one | 4.86 | 487.3 |
| 5-{4-[(Pyrimidin-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one | 4.53 | 402.3 |
| 5-{4-[(Pyrazin-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one | 4.42 | 402.1 |
| N-(4-Fluoro-3-{[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-methyl}-phenyl)-N-methyl-methanesulfonamide | 5.55 | 523.3 |
| 5-{4-[(1-Methanesulfonyl-piperidin-3-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one | 5.17 | 485.3 |
| 5-{4-[(4-Isobutyryl-morpholin-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one | 5.03 | 479.2 |
| 5-[4-(3,3-Dimethyl-2-oxo-butylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one | 6.00 | 408.2 |
| 5-[4-(1,2-Dimethyl-propylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one | 6.65 | 380.3 |
| 5-[4-(2-Methoxy-1-methyl-ethylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one | 5.57 | 382.3 |
| 5-{4-[2-(1,1-Dioxo-1D$^6$-isothiazolidin-2-yl)-ethylamino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one | 4.59 | 457.3 |
| 5-[4-(3-Methylamino-propylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one | 3.47 | 381.3 |

| Compound Name | HPLC Retention Time (min.) | MS Data (M+H) |
|---|---|---|
| 5-{4-[(Pyridin-3-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one | 4.62 | 401.3 |
| 5-{4-[(6-Methanesulfonyl-pyridin-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one | 4.89 | 479.3 |
| 5-{4-[3-(1,1-Dioxo-1,l,6-isothiazolidin-2-yl)-benzylamino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one | 5.45 | 519.2 |
| 5-[4-(1R-Phenyl-ethylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one | 6.42 | 414.4 |
| 5-(4-Isopropylamino-5-trifluoromethyl-pyrimidin-2-ylamino)-1,3-dihydro-indol-2-one | 5.84 | 352.2 |
| 5-(4R-sec-Butylamino-5-trifluoromethyl-pyrimidin-2-ylamino)-1,3-dihydro-indol-2-one | 6.22 | 366.2 |
| 5-(4S-sec-Butylamino-5-trifluoromethyl-pyrimidin-2-ylamino)-1,3-dihydro-indol-2-one | 6.23 | 366.2 |
| 5-[4-(2-Methylamino-ethylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one | 3.29 | 367.3 |
| 5-[4-(1S-Phenyl-ethylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one | 6.42 | 414.3 |
| 5-{4-[(2-Methanesulfonylmethyl-thiazol-4-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one | 4.72 | 499.3 |
| 5-(4-Propylamino-5-trifluoromethyl-pyrimidin-2-ylamino)-1,3-dihydro-indol-2-one | 5.91 | 352.2 |
| 5-[4-(2-Hydroxy-1-methyl-ethylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one | 4.49 | 368.2 |
| 5-[4-(1-Hydroxymethyl-propylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one | 4.85 | 382.2 |
| 5-{4-[(5-Methanesulfonyl-pyridin-3-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one | 4.55 | 479.4 |
| 5-{4-[(Pyridin-4-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one | 4.49 | 401.2 |
| 5-[4-(1,3-Dimethyl-butylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one | 6.99 | 394.3 |
| N-Isopropyl-N-{3-[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-propyl}-methanesulfonamide | 5.12 | 487.3 |
| 5-[4-(1S-Hydroxymethyl-2-methyl-propylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one | 5.23 | 396.3 |
| N-Cyclohexyl-N-{3-[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]- | 6.24 | 527.2 |

| Compound Name | HPLC Retention Time (min.) | MS Data (M+H) |
|---|---|---|
| propyl}-methanesulfonamide | | |
| 5-[4-(1,2,3,4-Tetrahydro-naphthalen-1-ylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one | 440.4 | 7.17 |
| 5-{4-[(1-Methanesulfonyl-pyrrolidin-2S-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one | 5.07 | 471.2 |
| 5-{4-[(3-Methyl-thiophen-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one | 6.18 | 420.4 |
| 5-{4-[(1-Methanesulfonyl-pyrrolidin-3R-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one | 4.95 | 471.2 |
| 5-[4-(2-Hydroxy-1S-phenyl-ethylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one | 5.28 | 430.3 |
| 5-[4-(2-Hydroxy-1S-methyl-ethylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one | 4.49 | 368.3 |
| 5-[4-(1R-Hydroxymethyl-propylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one | 4.85 | 382.2 |
| 5-[4-(1-Pyrimidin-4-yl-ethylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one | 4.84 | 416.3 |
| 5-[4-(1,1-Dioxo-tetrahydro-1-thiophen-3-ylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one | 4.67 | 426.3 |
| 5-{4-[(1H-Imidazol-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one | 3.27 | 390.3 |
| 5-[4-(2-Piperidin-2-yl-ethylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one | 3.79 | 421.4 |
| 5-[4-(Isobutyl-methyl-amino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one | 6.82 | 380.3 |
| N-Methyl-N-(3-{[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-methyl}-phenyl)-methanesulfonamide | 5.49 | 507.4 |
| N-Ethyl-N-(3-{[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-methyl}-phenyl)-methanesulfonamide | 5.67 | 521.3 |
| 5-[4-(2-Methanesulfonyl-benzylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one | 5.47 | 478.2 |
| N-Isopropyl-N-(3-{[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-methyl}-phenyl)-methanesulfonamide | 5.81 | 535.3 |
| 5-[4-[(3,4,5,6-Tetrahydro-2H-[1,2']bipyridinyl-3- | 5.79 | 484.3 |

| Compound Name | HPLC Retention Time (min.) | MS Data (M+H) |
|---|---|---|
| ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one | | |
| 5-{4-[(1-Pyrimidin-2-yl-piperidin-3-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one | 6.17 | 485.3 |
| 5-{4-[2R-(1-Methanesulfonyl-piperidin-2-yl)-ethylamino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one | 5.70 | 499.4 |
| 5-{4-[2S-(1-Methanesulfonyl-piperidin-2-yl)-ethylamino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one | 5.70 | 499.4 |
| 5-[4-(3-Methylsulfanyl-propylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one | 5.83 | 398.2 |
| 5-[4-(1S-Hydroxymethyl-3-methylsulfanyl-propylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one | 5.02 | 428.2 |
| 5-[4-(2-Hydroxy-1R-methyl-ethylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one | 4.49 | 368.3 |
| 5-[4-(1R-Hydroxymethyl-2-methyl-propylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one | 5.23 | 396.4 |
| N-Ethyl-N-{3-[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-propyl}-methanesulfonamide | 5.31 | 473.3 |
| 5-{4-[(1-Methanesulfonyl-pyrrolidin-3R-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one | 4.94 | 471.4 |
| 5-[4-(1S-Hydroxymethyl-propylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one | 4.86 | 382.3 |
| 5-[4-(3,5-Dinitro-benzylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one | 6.04 | 490.1 |
| N-(2-{[2-(2-Oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-methyl}-phenyl)-methanesulfonamide | 5.84 | 493.1 |
| N-Isopropyl-N-(2-[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-ethyl}-methanesulfonamide | 5.37 | 473.3 |
| 5-[4-(2-Hydroxy-1-phenyl-ethylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one | 5.29 | 430.3 |
| 5-[4-(1R-Hydroxymethyl-3-methyl-butylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one | 5.59 | 410.4 |
| 5-[4-(1S-Hydroxymethyl-3-methyl-butylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one | 5.59 | 410.4 |

| Compound Name | HPLC Retention Time (min.) | MS Data (M+H) |
|---|---|---|
| 5-{4-[(1-Methanesulfonyl-piperidin-2S-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one | 5.16 | 485.3 |
| 5-{4-[(1-Methanesulfonyl-pyrrolidin-2R-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one | 5.08 | 471.3 |
| 5-[4-(Methyl-pyridin-2-ylmethyl-amino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one | 5.37 | 415.3 |
| 5-{4-[(3-Methanesulfonyl-benzyl)-methyl-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one | 5.66 | 492.3 |
| N-Methyl-N-(2-{[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-methyl}-phenyl)-methanesulfonamide | 5.63 | 507.3 |
| 5-[4-(Methyl-pyridin-3-ylmethyl-amino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one | 5.25 | 415.4 |
| 5-{4-[(1-Methanesulfonyl-piperidin-3-ylmethyl)-methyl-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one | 5.69 | 499.4 |
| 5-[4-(Methyl-pyridin-4-ylmethyl-amino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one | 5.12 | 415.3 |
| 5-(4-Cyclopentylamino-5-trifluoromethyl-pyrimidin-2-ylamino)-1,3-dihydro-indol-2-one | 6.47 | 378.3 |
| 5-[4-(2,6-Dimethoxy-benzylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one | 6.78 | 460.3 |
| 5-{4-[(1,5-Dimethyl-1H-pyrazol-3-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one | 4.99 | 418.3 |
| 5-[4-(2-Imidazol-1-yl-ethylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one | 3.58 | 404.2 |
| 5-{4-[(Pyridin-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one | 4.95 | 401.4 |
| 5-[5-Trifluoromethyl-4-(2-trifluoromethyl-benzylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one | 6.57 | 468.2 |
| 5-{4-[(3-Methyl-pyridin-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one | 6.07 | 415.3 |
| 5-[4-(3-Methanesulfonyl-benzylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one | 5.16 | 478.2 |
| 5-{4-[2-(1-Acetyl-piperidin-2-yl)-ethylamino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2- | 5.22 | 463.4 |

| Compound Name | HPLC Retention Time (min.) | MS Data (M+H) |
|---|---|---|
| one | | |
| 5-{4-[2-(1-Propionyl-piperidin-2-yl)-ethylamino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one | 5.65 | 477.4 |
| 5-{4-[2-(1-Cyclopropanecarbonyl-piperidin-2-yl)-ethylamino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one | 5.86 | 489.4 |
| 5-{4-[2-(1-Isobutyryl-piperidin-2-yl)-ethylamino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one | 6.07 | 491.3 |
| 5-{4-[2-(1-Butyryl-piperidin-2-yl)-ethylamino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one | 5.99 | 491.4 |
| 5-{4-[2-(1-Methoxyacetyl-piperidin-2-yl)-ethylamino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one | 5.19 | 493.4 |
| 5-{4-[2-(1-Cyclobutanecarbonyl-piperidin-2-yl)-ethylamino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one | 6.31 | 503.4 |
| N-Methyl-N-{3-[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-propyl}-acetamide | 4.47 | 423.3 |
| N-Methyl-N-{3-[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-propyl}-propionamide | 4.89 | 437.45 |
| Cyclopropanecarboxylic acid methyl-{3-[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-propyl}-amide | 5.07 | 449.3 |
| N-Methyl-N-{3-[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-propyl}-isobutyramide | 5.24 | 451.3 |
| N-Methyl-N-{3-[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-propyl}-butyramide | 5.25 | 451.4 |
| 2-Methoxy-N-methyl-N-{3-[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-propyl}-acetamide | 4.47 | 453.3 |
| Cyclobutanecarboxylic acid methyl-{3-[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-propyl}-amide | 5.48 | 463.4 |
| 2,2,N-Trimethyl-N-{3-[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-propyl}-propionamide | 5.80 | 465.3 |
| 2,N-Dimethyl-N-{3-[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-propyl}-butyramide | 5.55 | 465.3 |
| N-Methyl-N-{3-[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-propyl}-benzamide | 5.38 | 485.3 |

| Compound Name | HPLC Retention Time (min.) | MS Data (M+H) |
|---|---|---|
| Isoxazole-5-carboxylic acid methyl-{3-[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-propyl}-amide | 4.91 | 476.2 |
| Morpholine-4-carboxylic acid methyl-{3-[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-propyl}-amide | 4.78 | 494.3 |
| Ethanesulfonic acid methyl-{3-[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-propyl}-amide | 5.29 | 473.3 |
| Propane-1-sulfonic acid methyl-{3-[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-propyl}-amide | 5.71 | 487.3 |
| 1,1,3-Trimethyl-3-{3-[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-propyl}-sulfonylurea | 5.53 | 488.3 |
| 2,2,2-Trifluoro-N-methyl-N-{3-[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-propyl}-acetamide | 5.80 | 477.2 |
| N-Methyl-N-{2-[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-ethyl}-acetamide | 4.23 | 409.2 |
| N-Methyl-N-{2-[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-ethyl}-propionamide | 4.61 | 423.2 |
| Cyclopropanecarboxylic acid methyl-{2-[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-ethyl}-amide | 4.77 | 435.2 |
| N-Methyl-N-{2-[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-ethyl}-isobutyramide | 4.94 | 437.2 |
| N-Methyl-N-{2-[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-ethyl}-butyramide | 4.95 | 437.2 |
| 2-Methoxy-N-methyl-N-{2-[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-ethyl}-acetamide | 4.21 | 439.2 |
| Cyclobutanecarboxylic acid methyl-{2-[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-ethyl}-amide | 5.17 | 449.3 |
| 2,2,N-Trimethyl-N-{2-[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-ethyl}-propionamide | 5.57 | 451.4 |
| 2,N-Dimethyl-N-{2-[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-ethyl}-butyramide | 5.26 | 451.4 |
| N-Methyl-N-{2-[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-ethyl}-benzamide | 4.80 | 471.3 |
| Isoxazole-5-carboxylic acid methyl-{2-[2-(2-oxo- | 4.51 | 462.3 |

| Compound Name | HPLC Retention Time (min.) | MS Data (M+H) |
|---|---|---|
| 2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino)-ethyl)-amide | | |
| Morpholine-4-carboxylic acid methyl-{2-[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-ethyl}-amide | 4.41 | 480.3 |
| N-Methyl-N-{2-[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-ethyl}-methanesulfonamide | 4.77 | 445.1 |
| Ethanesulfonic acid methyl-{2-[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino)-ethyl}-amide | 5.03 | 459.2 |
| Propane-1-sulfonic acid methyl-{2-[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-ethyl}-amide | 5.44 | 473.3 |
| 1,1,3-Trimethyl-3-{2-[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-ethyl}-sulfonylurea | 5.49 | 474.2 |
| 2,2,2-Trifluoro-N-methyl-N-{2-[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-ethyl}-acetamide | 5.49 | 463.2 |
| 5-[4-(2-Hydroxy-ethylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]- 1,3-dihydro-indol-2-one | 4.05 | 354.3 |
| 5-(4-Cyclopropylamino-5-trifluoromethyl-pyrimidin-2-ylamino)-1,3-dihydro-indol-2-one | 5.41 | 350.3 |
| 5-(4-Cyclobutylamino-5-trifluoromethyl-pyrimidin-2-ylamino)-1,3-dihydro-indol-2-one | 6.01 | 364.3 |
| 5-[4-(1,4-Dimethyl-pentylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one | 7.45 | 408.4 |
| 5-[4-(3-Imidazol-1-yl-propylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one | 3.77 | 418.3 |
| 5-[4-(2-Phenoxy-ethylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]- 1,3-dihydro-indol-2-one | 6.34 | 430.3 |
| 5-[4-(1-Cyclohexyl-ethylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one | 7.61 | 420.4 |
| 5-[4-(1-Hydroxymethyl-2,2-dimethyl-propylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one | 5.64 | 410.4 |
| 5-[4-(1-Methoxymethyl-propylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one | 5.96 | 396.3 |
| 5-[4-(Indan-2-ylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one | 6.78 | 426.4 |
| 5-[4-(1,2,3,4-Tetrahydro-naphthalen-1-ylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one | 7.16 | 440.3 |
| 5-(4-Cycloheptylamino-5-trifluoromethyl-pyrimidin-2-ylamino)-1,3-dihydro-indol-2-one | 7.21 | 406.3 |

| Compound Name | HPLC Retention Time (min.) | MS Data (M+H) |
|---|---|---|
| 5-{4-[2-(2-Oxo-imidazolidin-1-yl)-ethylamino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one | 4.04 | 422.3 |
| 4-[2-(2-Oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-butyric acid ethyl ester | 5.65 | 424.2 |
| 5-[4-(2-Hydroxy-1-hydroxymethyl-ethylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one | 3.72 | 384.2 |
| 5-[4-(3-Hydroxy-2,2-dimethyl-propylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one | 5.09 | 396.3 |
| 5-{4-[(Isochroman-1-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1;3-dihydro-indol-2-one | 6.36 | 456.3 |
| 5-[4-(4-Hydroxy-1,1-dioxo-tetrahydro-1&-thiophen-3-ylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one | 4.42 | 442.2 |
| 5-[4-(2-Methoxy-1-methyl-ethylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one | 5.58 | 382.3 |
| 5-[4-(*trans*-4-Methylsulfanyl-tetrahydro-furan-3-ylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one | 5.37 | 426.3 |
| 5-{4-[*trans*-2-(Pyrimidin-2-ylsulfanyl)-cyclopentylamino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one | 6.32 | 488.3 |
| 5-[4-(Indan-1-ylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one | 6.86 | 426.3 |
| 5-{4-[2-(2-Hydroxy-ethylsulfanyl)-ethylamino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one | 4.66 | 414.3 |
| 5-{4-[2-(Pyridin-3-yloxy)-propylamino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one | 5.20 | 445.3 |
| 5-{4-[2-(6-Methyl-pyridin-2-yl)-ethylamino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one | 5.00 | 429.3 |
| 5-{4-[(2,3-Dihydro-benzo[1,4]dioxin-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one | 5.01 | 458.2 |
| 5-{4-[(1-Methyl-1H-pyrazol-4-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one | 4.60 | 404.3 |
| 5-{4-[(4,5,6,7-Tetrahydro-benzothiazol-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one | 5.93 | 461.2 |
| 5-[4-(1-Phenyl-3-[1,2,4]triazol-1-yl-propylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol- | 5.24 | 495.2 |

| Compound Name | HPLC Retention Time (min.) | MS Data (M+H) |
|---|---|---|
| 2-one | | |
| 5-(4-Isobutylamino-5-trifluoromethyl-pyrimidin-2-ylamino)-1,3-dihydro-indol-2-one | 6.12 | 366.4 |
| 5-[4-(2-Cyclohexyl-1-hydroxymethyl-ethylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one | 6.41 | 450.4 |
| 2-[2-(2-Oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-propionic acid methyl ester | 5.26 | 396.3 |
| 5-(4-Cyclohexylamino-5-trifluoromethyl-pyrimidin-2-ylamino)-1,3-dihydro-indol-2-one | 6.82 | 392.3 |
| 5-[4-(3-Hydroxy-propylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one | 4.24 | 368.3 |
| 5-{4-[2-(4-Methyl-1H-imidazol-2-yl)-ethylamino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one | 3.54 | 418.3 |
| 5-[4-(Tetrahydro-furan-3-ylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one | 4.89 | 380.3 |
| 5-[4-(Dicyclopropylmethyl-amino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one | 6.59 | 404.3 |
| 5-{4-[2-(5-Methyl-4H-[1,2,4]triazol-3-yl)-ethylamino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one | 4.00 | 419.3 |
| 5-[4-(2-Ethylsulfanyl-ethylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one | 5.99 | 398.3 |
| 5-[4-(2-Phenoxy-propylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]- 1,3-dihydro-indol-2-one | 6.57 | 444.2 |
| 5-{4-[(1-Ethyl-5-oxo-pyrrolidin-3-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one | 4.57 | 435.2 |
| 5-(4-{[1-(2-Methoxy-ethyl)-5-oxo-pyrrolidin-3-ylmethyl]-amino}-5-trifluoromethyl-pyrimidin-2-ylamino)-1,3-dihydro-indol-2-one | 4.44 | 465.2 |
| 5-[4-(Benzhydryl-amino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one | 7.26 | 476.2 |
| 5-{4-[2-(1-Methyl-1H-pyrazol-4-yl)-ethylamino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one | 4.90 | 418.3 |
| 5-{4-[(4-Methyl-1H-imidazol-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one | 3.40 | 404.2 |
| 5-{4-[(5-Cyclopropyl-1H-pyrazol-3-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one | 5.00 | 430.2 |
| 5-{4-[2-(4-Methyl-thiazol-5-yl)-ethylamino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2- | 5.18 | 435.2 |

| Compound Name | HPLC Retention Time (min.) | MS Data (M+H) |
|---|---|---|
| one | | |
| 5-{4-[2-(1H-Benzoimidazol-2-yl)-ethylamino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one | 4.39 | 454.2 |
| 5-{4-[(5-Methyl-[1,3,4]oxadiazol-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one | 4.25 | 406.3 |
| 5-{4-[(5-Phenyl-4H-[1,2,4]triazol-3-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one | 4.92 | 467.3 |
| 5-{4-[(1H-Indol-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one | 6.10 | 439.3 |
| 5-{4-[(1,5-Dimethyl-1H-pyrazol-4-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one | 4.77 | 418.3 |
| 5-{4-[(Benzothiazol-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one | 5.77 | 457.2 |
| 5-{4-[(3-Methyl-isoxazol-5-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one | 5.02 | 405.3 |
| 5-{4-[(4-Methyl-thiazol-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one | 5.12 | 421.2 |
| 5-{4-[1-(4-Methyl-thiazol-2-yl)-ethylamino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one | 5.62 | 435.2 |
| 5-{5-Trifluoromethyl-4-[(1,3,5-trimethyl-1H-pyrazol-4-ylmethyl)-amino]-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one | 4.95 | 432.2 |
| 5-{4-[1-(2-Methyl-thiazol-4-yl)-ethylamino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one | 5.69 | 435.3 |
| 5-{4-[(3-Methyl-imidazo[2,1-b]thiazol-6-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one | 5.03 | 460.3 |
| 5-{4-[1-(5-Methyl-4H-[1,2,4]triazol-3-yl)-ethylamino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one | 4.20 | 419.3 |
| 5-{4-[1-(3,5-Dimethyl-1H-pyrazol-4-yl)-ethylamino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one | 5.02 | 432.3 |
| 5-{4-[2-(3,5-Dimethyl-1H-pyrazol-4-yl)-ethylamino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one | 4.85 | 432.4 |
| 5-{4-[2-(4,6-Dimethyl-pyrimidin-2-yl)-ethylamino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one | 5.17 | 444.4 |

| Compound Name | HPLC Retention Time (min.) | MS Data (M+H) |
|---|---|---|
| 5-{4-[2-(4-Methyl-5,6,7,8-tetrahydro-quinazolin-2-yl)-ethylamino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one | 5.88 | 484.4 |
| 5-[4-(2-Thiazol-4-yl-ethylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one | 5.18 | 421.3 |
| 5-(4-Dimethylamino-5-trifluoromethyl-pyrimidin-2-ylamino)-1,3-dihydro-indol-2-one | 5.60 | 338.3 |
| 5-{4-[(1-Pyrimidin-2-yl-piperidin-3-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one | 6.17 | 485.4 |
| 5-[4-(Indan-1-ylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one | 6.85 | 426.3 |

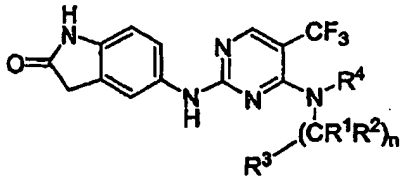
* * *

The present invention is not to be limited in scope by the specific embodiments described herein. Indeed, various modifications of the invention in addition to those described herein will become apparent to those skilled in the art from the foregoing description and the accompanying figures. Such modifications are intended to fall within the scope of the appended claims.

All patents, applications, publications, test methods, literature, and other materials cited herein are hereby incorporated herein by reference in their entireties.

## CLAIMS

1. A compound of the formula 1



1

or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof,

wherein n is an integer from 1 to 3;

each $R^1$ is a substituent independently selected from the group consisting of hydrogen, hydroxy, -($C_1$-$C_6$)alkyl, -($C_3$-$C_7$)cycloalkyl, -($C_2$-$C_9$)heterocyclyl, -O($C_1$-$C_6$)alkyl, -O($C_3$-$C_7$)cycloalkyl, -O($C_2$-$C_9$)heterocyclyl, -$NR^5R^6$, -$SR^7$, -$SOR^7$, -$SO_2R^7$, -$CO_2R^5$, -$CONR^5R^6$, -$SO_2NR^5R^6$, -$NHCOR^5$, -$NR^5CONR^5R^6$, and -$NR^5SO_2R^7$; with the proviso that a heteroatom of the foregoing $R^1$ substituents may not be bound to an $sp^3$ carbon atom bound to another heteroatom; and said $R^1$ substituents, -($C_1$-$C_6$)alkyl, -($C_3$-$C_7$)cycloalkyl, -($C_2$-$C_9$)heterocyclyl, -O($C_1$-$C_6$)alkyl, -O($C_3$-$C_7$)cycloalkyl, -O($C_2$-$C_9$)heterocyclyl, -$NR^5R^6$, -$SR^7$, -$SOR^7$, -$SO_2R^7$, -$CO_2R^5$, -$CONR^5R^6$, -$SO_2NR^5R^6$, -$NHCOR^5$, -$NR^5CONR^5R^6$, and -$NR^5SO_2R^7$ groups are optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -$CF_3$, -CN, -($C_1$-$C_6$)alkyl, -$NR^5R^6$, -$OR^5$, -($C_3$-$C_7$)cycloalkyl, -($C_2$-$C_9$)heterocyclyl, -$CO_2R^5$, -$CONR^5R^6$ and-$CONR^5R^6$; with the proviso that a heteroatom of the foregoing optional $R^1$ moieties may not be bound to an $sp^3$ carbon atom bound to another heteroatom;

each $R^2$ is a substituent independently selected from the group consisting of hydrogen, -($C_1$-$C_6$)alkyl, -($C_2$-$C_6$)alkenyl, -($C_2$-$C_6$)alkynyl, -($C_3$-$C_7$)cycloalkyl, -($C_2$-$C_9$)heterocyclyl, -$CO_2R^5$, and -$CONR^5R^6$; with the proviso that a heteroatom of any of the foregoing $R^2$ substituents may not be bound to an $sp^3$ carbon atom that is bound to another heteroatom; and said $R^2$ substituents, -($C_1$-$C_6$)alkyl, -($C_2$-$C_6$)alkenyl, -($C_2$-$C_6$)alkynyl, -($C_3$-$C_7$)cycloalkyl, -($C_2$-$C_9$)heterocyclyl, -$CO_2R^5$, and -$CONR^5R^6$, are optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -$CF_3$, -$NO_2$, -CN, -($C_1$-$C_6$)alkyl, -($C_2$-$C_6$)alkenyl, -($C_2$-$C_6$)alkynyl, -C=N-OH, -C=N-O(($C_1$-$C_6$)alkyl), -$NR^5R^6$, -$OR^5$, -($C_3$-$C_7$)cycloalkyl, -($C_2$-$C_9$)heterocyclyl, -$CO_2R^5$, -$CONR^5R^6$, -$CONR^5R^6$, -$SR^7$, -$SOR^7$, -$SO_2R^7$, -$SO_2NR^5R^6$, -$NHCOR^5$, -$NR^5CONR^5R^6$, and -$NR^5SO_2R^7$, wherein said –($C_2$-$C_6$)alkenyl and –($C_2$-$C_6$)alkynyl $R^2$ moieties may be optionally substituted by one to three $R^6$ groups; and with the proviso that a heteroatom of the foregoing optional $R^2$ moieties may not be bound to an $sp^3$ carbon atom bound to another heteroatom;

$R^1$ and $R^2$ may be taken together with the atom(s) to which they are attached to form a cyclic group, -($C_3$-$C_{10}$)cycloalkyl or -($C_2$-$C_9$)heterocyclyl, wherein said cyclic group is optionally substituted by one to three moieties selected from the group consisting of hydrogen, halogen, hydroxy, $-CF_3$, $-NO_2$, -CN, -($C_1$-$C_8$)alkyl, -($C_2$-$C_8$)alkenyl, -($C_2$-$C_8$)alkynyl, -C=N-OH, -C=N-O(($C_1$-$C_8$)alkyl), $-NR^5R^6$, $-OR^5$, -($C_3$-$C_7$)cycloalkyl, -($C_2$-$C_8$)heterocyclyl, $-CO_2R^5$, $-CONR^5R^6$, $-CONR^5R^6$, $-SR^7$, $-SOR^7$, $-SO_2R^7$, $-SO_2NR^5R^6$, $-NHCOR^5$, $-NR^5CONR^5R^6$, and $-NR^6SO_2R^7$, wherein said –($C_2$-$C_8$)alkenyl and –($C_2$-$C_8$)alkynyl moieties of said cyclic group may be optionally substituted by one to three $R^5$ groups, and said cyclic group is optionally interrupted by one to three elements selected from the group consisting of –(C=O), $-SO_2$, -S-, -O-, -N-, -NH- and $-NR^5$, with the proviso that any of the foregoing cyclic group moieties or elements may not be bound to an $sp^3$ carbon atom that is bound to another heteroatom;

$R^3$ is a substituent selected from the group consisting of:

(a) hydrogen;

(b) -($C_6$-$C_{10}$)aryl or -($C_1$-$C_9$)heteroaryl, optionally substituted by one to three moieties independently selected from the group consisting of halogen, hydroxy, -($C_1$-$C_8$)alkyl, -($C_1$-$C_8$)alkyl-P(O)(O($C_1$-$C_8$)alkyl)$_2$, -($C_3$-$C_{10}$)cycloalkyl, ($C_6$-$C_{10}$)aryl, ($C_2$-$C_9$)heterocyclyl, -($C_1$-$C_8$)heteroaryl, $-NR^5R^6$, $-NHSO_2$($C_1$-$C_8$)alkyl, $-NHSO_2$($C_3$-$C_8$)cycloalkyl, -N(($C_1$-$C_8$)alkyl)($SO_2$-$C_1$-$C_8$)alkyl), -N(($C_1$-$C_8$)alkyl)($SO_2$($C_3$-$C_8$)cycloalkyl), -O($C_1$-$C_8$)alkyl, $-O-SO_2$($C_1$-$C_8$)alkyl, -(CO)($C_1$-$C_8$)alkyl, $-(CO)CF_3$, -(CO)($C_3$-$C_{10}$)cycloalkyl, -(CO)($C_6$-$C_{10}$)aryl, -(CO)($C_2$-$C_9$)heterocyclyl, -(CO)($C_1$-$C_9$)heteroaryl, -(CO)O($C_1$-$C_8$)alkyl, -(CO)O($C_3$-$C_{10}$)cycloalkyl, -(CO)O($C_6$-$C_{10}$)aryl, -(CO)O($C_2$-$C_9$)heterocyclyl, -(CO)O($C_1$-$C_9$)heteroaryl, -(CO)($C_1$-$C_8$)alkyl-O($C_1$-$C_8$)alkyl, $-SO_2$($C_1$-$C_8$)alkyl, $-SO_2$($C_3$-$C_8$)cycloalkyl, $SO_2CF_3$, $SO_2NH_2$, $SO_2NH$($C_1$-$C_8$)alkyl, $-SO_2NH$($C_3$-$C_8$)cycloalkyl, $-SO_2N$(($C_1$-$C_8$)alkyl)$_2$, $-SO_2N$(($C_3$-$C_8$)cycloalkyl)$_2$, $-SO_2NR^5R^6$, and $-SO_2N$($C_1$-$C_8$)alkyl-($C_6$-$C_{10}$)aryl; wherein said -($C_6$-$C_{10}$) aryl or -($C_1$-$C_9$) heteroaryl are optionally interrupted by one to three elements selected from the group consisting of –(C=O), $-SO_2$, -S-, -O-, -N-, -NH- and $-NR^5$; and $R^5$ and $R^6$ of said $NR^5R^6$ $R^3$(b) group may be taken together with the atoms to which they are attached to form a -($C_2$-$C_9$)heterocyclyl;

(c) -($C_3$-$C_{10}$)cycloalkyl, -($C_2$-$C_9$)heterocyclyl, and -($C_1$-$C_8$)alkyl-($C_2$-$C_9$) heterocyclyl, optionally substituted by one to three moieties independently selected from the group consisting of halogen, hydroxy, -($C_1$-$C_8$)alkyl, -($C_1$-$C_8$)alkyl-P(O)(O($C_1$-$C_8$)alkyl)$_2$, -($C_3$-$C_{10}$)cycloalkyl, ($C_6$-$C_{10}$)aryl, ($C_2$-$C_9$)heterocyclyl, -($C_1$-$C_9$)heteroaryl, $-NR^5R^6$, $-NSO_2$($C_1$-$C_8$)alkyl, $-NHSO_2$($C_3$-$C_8$)cycloalkyl, -N(($C_1$-$C_8$)alkyl)($SO_2$-$C_1$-$C_8$)alkyl), -N(($C_1$-$C_8$)alkyl)($SO_2$($C_3$-$C_8$)cycloalkyl), -O($C_1$-$C_8$)alkyl, $-O-SO_2$($C_1$-$C_8$)alkyl, $-O-SO_2$($C_1$-$C_8$)alkyl, -(CO)($C_1$-$C_8$)alkyl, $-(CO)CF_3$, -(CO)($C_3$-$C_{10}$)cycloalkyl, -(CO)($C_6$-$C_{10}$)aryl, -(CO)($C_2$-

$C_9$)heterocyclyl, -(CO)($C_1$-$C_9$)heteroaryl, -(CO)O($C_1$-$C_6$)alkyl, -(CO)O($C_3$-$C_{10}$)cycloalkyl, -(CO)O($C_6$-$C_{10}$)aryl, -(CO)O($C_2$-$C_9$)heterocyclyl, -(CO)O($C_1$-$C_9$)heteroaryl, -(CO)($C_1$-$C_6$)alkyl-O($C_1$-$C_6$)alkyl, -$SO_2$($C_1$-$C_6$)alkyl, -$SO_2$($C_3$-$C_6$)cycloalkyl, $SO_2CF_3$, $SO_2NH_2$, $SO_2NH$($C_1$-$C_6$)alkyl, -$SO_2NH$($C_3$-$C_6$)cycloalkyl, -$SO_2N$(($C_1$-$C_6$)alkyl)$_2$, -$SO_2N$(($C_3$-$C_6$)cycloalkyl)$_2$, -$SO_2NR^5R^6$, and -$SO_2N$($C_1$-$C_6$)alkyl-($C_6$-$C_{10}$)aryl; wherein said -($C_3$-$C_{10}$)cycloalkyl, -($C_2$-$C_9$)heterocyclyl, and -($C_1$-$C_6$)alkyl-($C_2$-$C_9$) heterocyclyl are optionally interrupted by one to three elements selected from the group consisting of –(C=O), -$SO_2$, -S-, -O-, -N-, -NH- and –$NR^5$; and $R^5$ and $R^6$ of said $NR^5R^6$ $R^3$(b) group may be taken together with the atoms to which they are attached to form a -($C_2$-$C_9$)heterocyclyl;

(d) -($C_1$-$C_6$)alkyl optionally substituted by one to three moieties selected from the group consisting of halogen, hydroxy, -($C_1$-$C_6$)alkyl, -($C_1$-$C_6$)alkyl-P(O)(O($C_1$-$C_6$)alkyl)$_2$, -($C_3$-$C_{10}$)cycloalkyl, ($C_6$-$C_{10}$)aryl, ($C_2$-$C_9$)heterocyclyl, -($C_1$-$C_9$)heteroaryl, -$NR^5R^6$, -$NSO_2$($C_1$-$C_6$)alkyl, -$NHSO_2$($C_3$-$C_6$)cycloalkyl, -N(($C_1$-$C_6$)alkyl)($SO_2$-$C_1$-$C_6$)alkyl), -N(($C_1$-$C_6$)alkyl)($SO_2$($C_3$-$C_6$)cycloalkyl), -O($C_1$-$C_6$)alkyl, -O-$SO_2$($C_1$-$C_6$)alkyl, -(CO)($C_1$-$C_6$)alkyl, -(CO)$CF_3$, -(CO)($C_3$-$C_{10}$)cycloalkyl, -(CO)($C_6$-$C_{10}$)aryl, -(CO)($C_2$-$C_9$)heterocyclyl, -(CO)($C_1$-$C_9$)heteroaryl, -(CO)O($C_1$-$C_6$)alkyl, -(CO)O($C_3$-$C_{10}$)cycloalkyl, -(CO)O($C_6$-$C_{10}$)aryl, -(CO)O($C_2$-$C_9$)heterocyclyl, -(CO)O($C_1$-$C_9$)heteroaryl, -(CO)($C_1$-$C_6$)alkyl-O($C_1$-$C_6$)alkyl, -$SO_2$($C_1$-$C_6$)alkyl, -$SO_2$($C_3$-$C_6$)cycloalkyl, $SO_2CF_3$, $SO_2NH_2$, $SO_2NH$($C_1$-$C_6$)alkyl, -$SO_2NH$($C_3$-$C_6$)cycloalkyl, -$SO_2N$(($C_1$-$C_6$)alkyl)$_2$, -$SO_2N$(($C_3$-$C_6$)cycloalkyl)$_2$, -$SO_2NR^5R^6$, and -$SO_2N$($C_1$-$C_6$)alkyl-($C_6$-$C_{10}$)aryl; wherein said -($C_1$-$C_6$)alkyl is optionally interrupted by one to three elements selected from the group consisting of –(C=O), -$SO_2$, -S-, -O-, -N-, -NH- and -$NR^5$; and $R^5$ and $R^6$ of said $NR^5R^6$ $R^3$(b) group may be taken together with the atoms to which they are attached to form a -($C_2$-$C_9$)heterocyclyl; and wherein each $R^3$ (b)-(d) substituent, moiety, or element is optionally substituted by one to three radicals independently selected from the group consisting of hydrogen, halogen, hydroxy, -$CF_3$, -$NO_2$, -CN, -($C_1$-$C_6$)alkyl, -($C_2$-$C_6$)alkenyl, -($C_2$-$C_6$)alkynyl, -($C_3$-$C_7$)cycloalkyl, -($C_2$-$C_9$)heterocyclyl, -($C_6$-$C_{10}$)aryl, -($C_1$-$C_9$)heteroaryl, -O($C_1$-$C_6$)alkyl, -O($C_3$-$C_7$)cycloalkyl, -O($C_2$-$C_9$)heterocyclyl, -C=N-OH, -C=N-O($C_1$-$C_6$ alkyl), -$NR^5R^6$, -$SR^7$, -$SOR^7$, -$SO_2R^7$, -$CO_2R^5$, -$CONR^5R^6$, -$SO_2NR^5R^6$, -$NHCOR^5$, -$NR^5CONR^5R^6$, and -$NR^5SO_2R^7$; with the proviso that a heteroatom of the foregoing $R^3$ (b)-(d) substituents, moieties, elements or radicals may not be bound to an $sp^3$ carbon atom bound to another heteroatom; and wherein $R^5$ and $R^6$ of said -$NR^5R^6$, -$CONR^6R^6$, -$SO_2NR^5R^6$, and -$NR^5CONR^5R^6$ groups may be taken together with the atoms to which they are attached to form a -($C_2$-$C_9$)heterocyclyl;

$R^4$ is a substituent selected from the group consisting of hydrogen, ($C_1$-$C_6$)alkyl, -($C_3$-$C_7$)cycloalkyl, and -($C_2$-$C_9$)heterocyclyl; wherein said ($C_1$-$C_6$)alkyl, -($C_3$-$C_7$)cycloalkyl, and -($C_2$-$C_9$)heterocyclyl $R^4$ substituents are optionally substituted by one to three moieties

independently selected from the group consisting of hydrogen, halogen, -($C_1$-$C_8$)alkyl, -CN, -$NR^5_2$, -$OR^5$, -($C_3$-$C_7$)cycloalkyl, -($C_2$-$C_9$)heterocyclyl, -$CO_2R^5$, and -$CONR^5R^6$; with the proviso that a heteroatom of the foregoing $R^4$ substituents may not be bound to an $sp^3$ carbon atom bound to another heteroatom; and wherein $R^5$ and $R^6$ of said -$CONR^5R^6$ group may be taken together with the atoms to which they are attached to form a -($C_3$-$C_{10}$)cycloalkyl or -($C_2$-$C_9$)heterocyclyl;

$R^5$ and $R^6$ are each substituents independently selected from the group consisting of hydrogen, -($C_1$-$C_8$)alkyl, -($C_3$-$C_7$)cycloalkyl, -($C_2$-$C_9$)heterocyclyl, -($C_6$-$C_{10}$)aryl, and -($C_1$-$C_9$)heteroaryl; wherein said -($C_1$-$C_8$)alkyl, -($C_3$-$C_7$)cycloalkyl, -($C_2$-$C_9$)heterocyclyl, -($C_6$-$C_{10}$)aryl, and -($C_1$-$C_9$)heteroaryl $R^5$ or $R^6$ substituents are optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, -$CF_3$, -CN, -($C_1$-$C_8$)alkyl, -NH($C_1$-$C_8$)alkyl, -NH($C_3$-$C_7$)cycloalkyl, -NH($C_2$-$C_9$)heterocyclyl, -NH($C_6$-$C_{10}$)aryl, -NH($C_1$-$C_9$)heteroaryl, -N(($C_1$-$C_8$)alkyl)$_2$, -N(($C_3$-$C_7$)cycloalkyl)$_2$, -N(($C_2$-$C_9$)heterocyclyl)$_2$, -N(($C_6$-$C_{10}$)aryl)$_2$, -N(($C_1$-$C_9$)heteroaryl)$_2$ , -O($C_1$-$C_8$)alkyl, -O($C_3$-$C_7$)cycloalkyl, -O($C_2$-$C_9$)heterocyclyl, -O($C_6$-$C_{10}$)aryl, -O($C_1$-$C_9$)heteroaryl, -($C_3$-$C_7$)cycloalkyl, -($C_2$-$C_9$)heterocyclyl, -$CO_2R^7$, -$CONH_2$, -$CONHR^7$, and -$CONR^7R^8$; with the proviso that a heteroatom of the foregoing $R^5$ or $R^6$ substituents or moieties may not be bound to an $sp^3$ carbon atom bound to another heteroatoms; and wherein $R^7$ and $R^8$ of said -$CONR^7R^8$ group may be taken together with the atoms to which they are attached to form a -($C_1$-$C_9$) heteroaryl;

$R^5$ and $R^6$ may be taken together with the atom(s) to which they are attached to form a cyclic group, -($C_3$-$C_{10}$)cycloalkyl or -($C_2$-$C_9$)heterocyclyl, wherein said cyclic group is optionally substituted by one to three moieties selected from the group consisting of hydrogen, halogen, hydroxy, -$CF_3$, -$NO_2$, -CN, -($C_1$-$C_8$)alkyl, -($C_2$-$C_8$)alkenyl, -($C_2$-$C_8$)alkynyl, -C=N-OH, -C=N-O(($C_1$-$C_8$)alkyl), -$NR^5R^6$, -$OR^5$, -($C_3$-$C_7$)cycloalkyl, -($C_2$-$C_9$)heterocyclyl, -$CO_2R^5$, -$CONR^5R^6$, -$CONR^5R^8$, -$SR^7$, -$SOR^7$, -$SO_2R^7$, -$SO_2NR^5R^6$, -NHCO$R^5$, -$NR^5CONR^5R^6$, and -$NR^5SO_2R^7$, wherein said –($C_2$-$C_8$)alkenyl and –($C_2$-$C_8$)alkynyl moieties of said cyclic group may be optionally substituted by one to three $R^7$ groups, and said cyclic group is optionally interrupted by one to three elements selected from the group consisting of –(C=O), -$SO_2$, -S-, -O-, -N-, -NH- and –$NR^5$, with the proviso that any of the foregoing cyclic group moieties or elements may not be bound to an $sp^3$ carbon atom that is bound to another heteroatom;

$R^7$ is a substituent selected from the group consisting of –($C_1$-$C_8$)alkyl, -($C_3$-$C_7$)cycloalkyl, -($C_2$-$C_9$)heterocyclyl, -($C_6$-$C_{10}$)aryl, and -($C_1$-$C_9$) heteroaryl; wherein said -($C_1$-$C_8$)alkyl, -($C_3$-$C_7$)cycloalkyl, -($C_2$-$C_9$)heterocyclyl, -($C_6$-$C_{10}$)aryl, and -($C_1$-$C_9$) heteroaryl $R^7$ substituents are optionally substituted by one to three moieties independently selected from

the group consisting of hydrogen, halogen, hydroxy, -CN, -($C_1$-$C_6$)alkyl, -$NR^8_2$, and -O($C_1$-$C_6$)alkyl, with the proviso that a heteroatom of the foregoing $R^7$ substituents or moieties may not be bound to an $sp^3$ carbon atom bound to another heteroatom;

$R^8$ is a substituent selected from the group consisting of hydrogen, -($C_1$-$C_6$)alkyl, -($C_3$-$C_7$)cycloalkyl, -($C_2$-$C_9$)heterocyclyl, -($C_6$-$C_{10}$)aryl, and -($C_1$-$C_9$) heteroaryl; wherein said -($C_1$-$C_6$)alkyl, -($C_3$-$C_7$)cycloalkyl, -($C_2$-$C_9$)heterocyclyl, -($C_6$-$C_{10}$)aryl, and -($C_1$-$C_9$) heteroaryl $R^8$ radicals are optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, -($C_1$-$C_6$)alkyl, -$NH_2$, -$NHR^9$, -$NR^9_2$, $OR^9$, -($C_3$-$C_7$)cycloalkyl, -($C_2$-$C_9$)heterocyclyl, -$CO_2R^{10}$, -$CONH_2$, -$CONHR^{10}$, and -$CONR^{10}R^{11}$; with the proviso that a heteroatom of the foregoing $R^8$ substituents or moieties may not be bound to an $sp^3$ carbon atom bound to another heteroatom; and wherein $R^{10}$ and $R^{11}$ of -$CONR^{10}R^{11}$ may be taken together with the atoms to which they are attached to form a -(C2-$C_9$)heterocyclyl;

$R^9$ and $R^{10}$ are each -($C_1$-$C_6$)alkyl and may be taken together with the atoms to which they are attached to form a -($C_2$-$C_9$)heterocyclyl; and

$R^{11}$ is hydrogen or -($C_1$-$C_6$)alkyl.

2. A compound of claim 1 wherein $R^1$ is selected from hydrogen, hydroxy, and -($C_1$-$C_6$)alkyl, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -CN, -($C_1$-$C_6$)alkyl, -$NR^5R^6$, -$OR^5$, -($C_3$-$C_7$)cycloalkyl, -($C_2$-$C_9$)heterocyclyl, -$CO_2R^5$, -$CONR^5R^6$ and-$CONR^5R^6$; $R^2$ is hydrogen or -($C_1$-$C_6$)alkyl, optionally substituted by one to three moieties independently selected from the group consisting of hydrogen, halogen, hydroxy, -$NO_2$, -CN, -($C_1$-$C_6$)alkyl, -($C_2$-$C_6$)alkenyl, -($C_2$-$C_6$)alkynyl, -C=N-OH, -C=N-O(($C_1$-$C_6$)alkyl), -$NR^5R^6$, -$OR^5$, -($C_3$-$C_7$)cycloalkyl, -($C_2$-$C_9$)heterocyclyl, -$CO_2R^6$, -$CONR^5R^6$, -$CONR^5R^6$, -$SR^7$, -$SOR^7$, -$SO_2R^7$, -$SO_2NR^5R^6$, -$NHCOR^6$, -$NR^5CONR^5R^6$, and -$NR^5SO_2R^7$, wherein said –($C_2$-$C_6$)alkenyl and –($C_2$-$C_6$)alkynyl $R^2$ moieties may be optionally substituted by one to three $R^5$ groups; and n is 1.

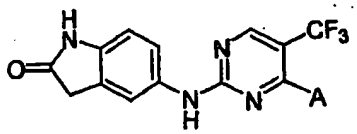
3. A compound of any of the preceding claims wherein $R^3$ is -($C_6$-$C_{10}$)aryl or -($C_1$-$C_9$)heteroaryl, optionally substituted by one to three moieties independently selected from the group consisting of halogen, hydroxy, -($C_1$-$C_6$)alkyl, -($C_1$-$C_6$)alkyl-P(O)(O($C_1$-$C_6$)alkyl)$_2$, -($C_3$-$C_{10}$)cycloalkyl, ($C_6$-$C_{10}$)aryl, ($C_2$-$C_9$)heterocyclyl, -($C_1$-$C_9$)heteroaryl, -$NR^5R^6$, -$NHSO_2$($C_1$-$C_6$)alkyl, -$NHSO_2$($C_3$-$C_6$)cycloalkyl, -N(($C_1$-$C_6$)alkyl)($SO_2$-$C_1$-$C_6$)alkyl), -N(($C_1$-$C_6$)alkyl)($SO_2$($C_3$-$C_6$)cycloalkyl), -O($C_1$-$C_6$)alkyl, -O-$SO_2$($C_1$-$C_6$)alkyl, -(CO)($C_1$-$C_6$)alkyl, -(CO)$CF_3$, -(CO)($C_3$-$C_{10}$)cycloalkyl, -(CO)($C_6$-$C_{10}$)aryl, -(CO)($C_2$-$C_9$)heterocyclyl, -(CO)($C_1$-$C_9$)heteroaryl, -(CO)O($C_1$-$C_6$)alkyl, -(CO)O($C_3$-$C_{10}$)cycloalkyl, -(CO)O($C_6$-$C_{10}$)aryl, -(CO)O($C_2$-$C_9$)heterocyclyl, -(CO)O($C_1$-$C_9$)heteroaryl, -(CO)($C_1$-$C_6$)alkyl-O($C_1$-$C_6$)alkyl, -$SO_2$($C_1$-$C_6$)alkyl,

$-SO_2(C_3-C_8)$cycloalkyl, $SO_2CF_3$, $SO_2NH_2$, $SO_2NH(C_1-C_8)$alkyl, $-SO_2NH(C_3-C_8)$cycloalkyl, $-SO_2N((C_1-C_8)alkyl)_2$, $-SO_2N((C_3-C_8)cycloalkyl)_2$, $-SO_2NR^5R^6$, and $-SO_2N(C_1-C_8)$alkyl-$(C_6-C_{10})$aryl; wherein said $-(C_6-C_{10})$ aryl or $-(C_1-C_9)$ heteroaryl are optionally interrupted by one to three elements selected from the group consisting of –(C=O), $-SO_2$, -S-, -O-, -N-, -NH- and $-NR^5$; and $R^5$ and $R^6$ of said $NR^5R^6$ $R^3$(b) group may be taken together with the atoms to which they are attached to form a $-(C_2-C_9)$heterocyclyl.

4. A compound of any of the preceding claims wherein $R^3$ is selected from $-(C_3-C_{10})$cycloalkyl, $-(C_2-C_9)$heterocyclyl, and $-(C_1-C_8)$alkyl-$(C_2-C_9)$ heterocyclyl, optionally substituted by one to three moieties independently selected from the group consisting of halogen, hydroxy, $-(C_1-C_8)$alkyl, $-(C_1-C_8)$alkyl-$P(O)(O(C_1-C_8)alkyl)_2$, $-(C_3-C_{10})$cycloalkyl, $(C_6-C_{10})$aryl, $(C_2-C_9)$heterocyclyl, $-(C_1-C_9)$heteroaryl, $-NR^5R^6$, $-NSO_2(C_1-C_8)$alkyl, $-NHSO_2(C_3-C_8)$cycloalkyl, $-N((C_1-C_8)alkyl)(SO_2-C_1-C_8)alkyl)$, $-N((C_1-C_8)alkyl)(SO_2(C_3-C_8)cycloalkyl)$, $-O(C_1-C_8)$alkyl, $-O-SO_2(C_1-C_8)$alkyl, $-O-SO_2(C_1-C_8)$alkyl, $-(CO)(C_1-C_8)$alkyl, $-(CO)CF_3$, $-(CO)(C_3-C_{10})$cycloalkyl, $-(CO)(C_6-C_{10})$aryl, $-(CO)(C_2-C_9)$heterocyclyl, $-(CO)(C_1-C_9)$heteroaryl, $-(CO)O(C_1-C_8)$alkyl, $-(CO)O(C_3-C_{10})$cycloalkyl, $-(CO)O(C_6-C_{10})$aryl, $-(CO)O(C_2-C_9)$heterocyclyl, $-(CO)O(C_1-C_9)$heteroaryl, $-(CO)(C_1-C_8)$alkyl-$O(C_1-C_8)$alkyl, $-SO_2(C_1-C_8)$alkyl, $-SO_2(C_3-C_8)$cycloalkyl, $SO_2CF_3$, $SO_2NH_2$, $SO_2NH(C_1-C_8)$alkyl, $-SO_2NH(C_3-C_8)$cycloalkyl, $-SO_2N((C_1-C_8)alkyl)_2$, $-SO_2N((C_3-C_8)cycloalkyl)_2$, $-SO_2NR^5R^6$, and $-SO_2N(C_1-C_8)$alkyl-$(C_6-C_{10})$aryl; wherein said $-(C_3-C_{10})$cycloalkyl, $-(C_2-C_9)$heterocyclyl, and $-(C_1-C_8)$alkyl-$(C_2-C_9)$ heterocyclyl are optionally interrupted by one to three elements selected from the group consisting of –(C=O), $-SO_2$, -S-, -O-, -N-, -NH- and $-NR^5$; and $R^5$ and $R^6$ of said $NR^5R^6$ $R^3$(b) group may be taken together with the atoms to which they are attached to form a $-(C_2-C_9)$heterocyclyl.

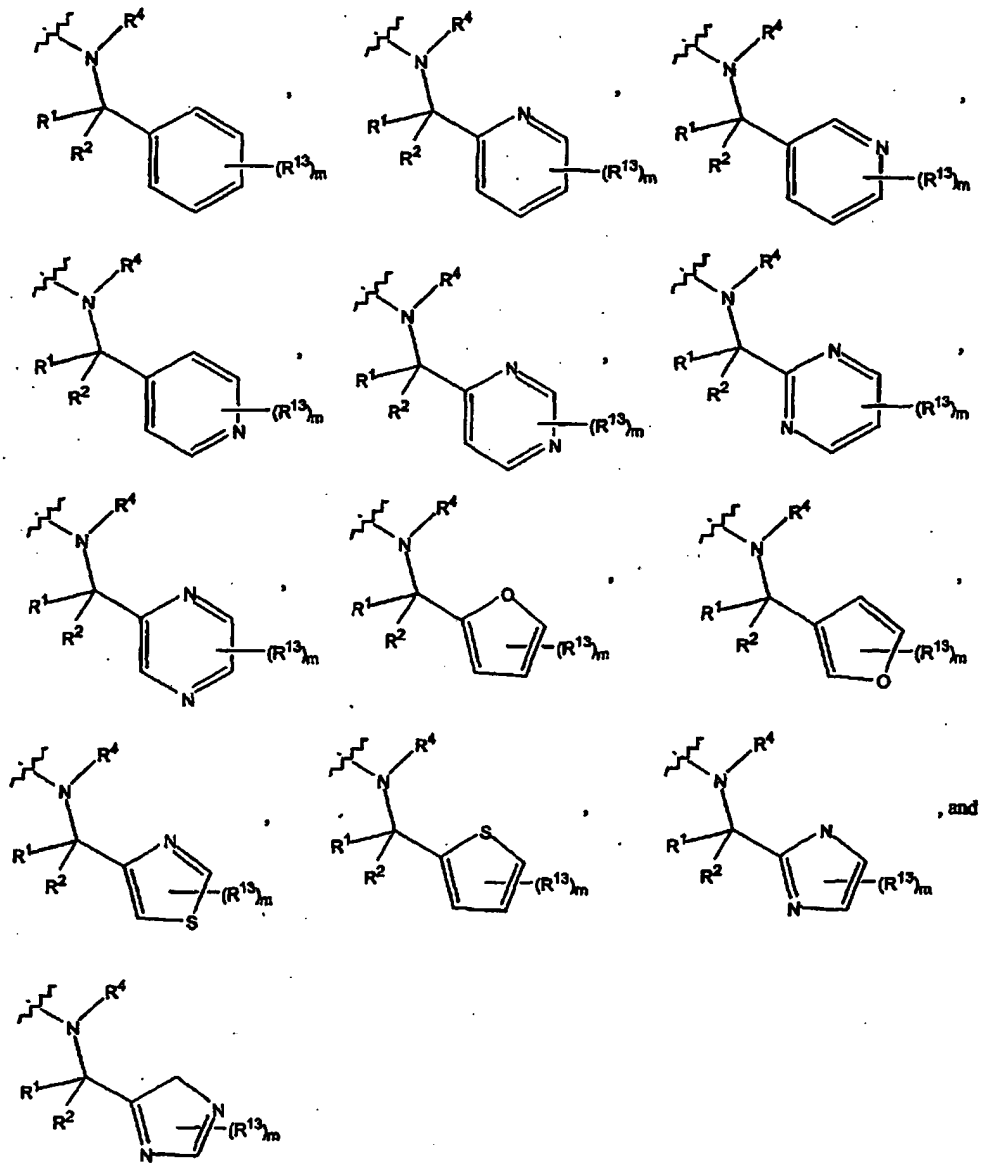
5. A compound of any of the preceding claims wherein $R^3$ is $-(C_1-C_8)$alkyl optionally substituted by one to three moieties selected from the group consisting of halogen, hydroxy, $-(C_1-C_8)$alkyl, $-(C_3-C_{10})$cycloalkyl, $-NSO_2(C_1-C_8)$alkyl, $-NHSO_2(C_3-C_8)$cycloalkyl, $-N((C_1-C_8)alkyl)(SO_2-C_1-C_8)alkyl)$, $-N((C_1-C_8)alkyl)(SO_2(C_3-C_8)cycloalkyl)$, $-O(C_1-C_8)$alkyl, $-O-SO_2(C_1-C_8)$alkyl, $-SO_2(C_1-C_8)$alkyl, $-SO_2(C_3-C_8)$cycloalkyl, $-SO_2NH_2$, $SO_2NH(C_1-C_8)$alkyl, $-SO_2NH(C_3-C_8)$cycloalkyl, $-SO_2N((C_1-C_8)alkyl)_2$, $-SO_2N((C_3-C_8)cycloalkyl)_2$, and $-SO_2NR^5R^6$.

6. A compound according to any of the preceding claims of the formula 2

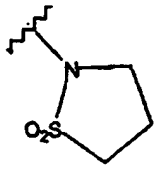


2

wherein A is selected from the group consisting of:



wherein m is an integer from 0-3 and $R^{13}$ is a substituent selected from the group consisting of hydrogen, halogen, hydroxy, $(C_1-C_6)$-alkyl, $(C_3-C_7)$-cycloalkyl, $(C_6-C_{10})$-aryl, $(C_1-C_9)$heteroaryl, $(C_2-C_9)$-heterocyclyl, O-$(C_1-C_6)$-alkyl, O-$(C_3-C_7)$-cycloalkyl, $SO_2$-$(C_1-C_6)$alkyl, $SO_2(C_3-C_7)$-cycloalkyl, $NHSO_2(C_1-C_6)$alkyl, $N((C_1-C_6)alkyl)(SO_2(C_1-C_6-alkyl))$, $N((C_3-C_7)cycloalkyl)(SO_2(C_1-C_6-alkyl))$, $N(C_1-C_6-alkyl)(SO_2(C_3-C_7)cycloalkyl)$, $N((C_3-C_7)cycloalkyl)(SO_2(C_3-C_7)cycloalkyl)$, $OSO_2(C_1-C_6)$alkyl, $SO_2CF_3$, $SO_2NH_2$, $SO_2NH(C_1-C_6)$alkyl, $SO_2NH(C_3-C_7)$cycloalkyl, $SO_2NR^5R^6$, $SO_2N((C_1-C_6)alkyl)_2$, $CF_3$, CO-$(C_1-C_6)$alkyl, CO-$(C_3-C_7)$cycloalkyl, $COCF_3$, $CO_2(C_1-C_6)$alkyl,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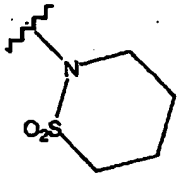
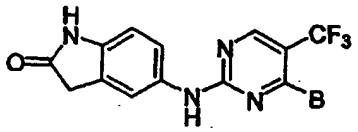
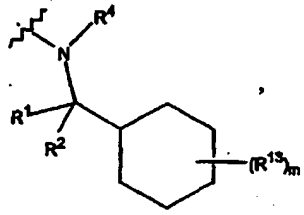
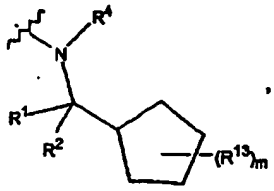
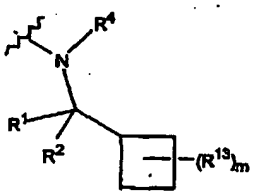
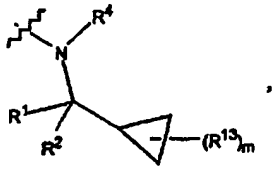
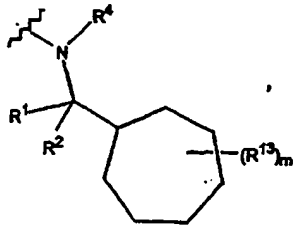
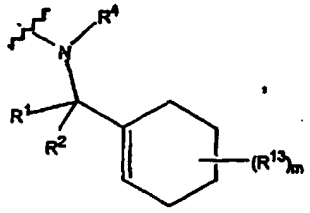
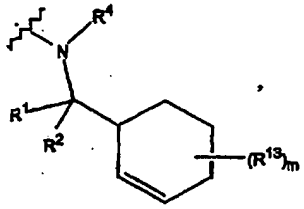
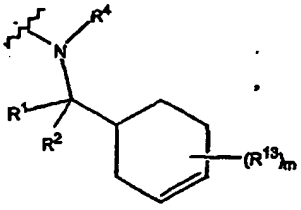
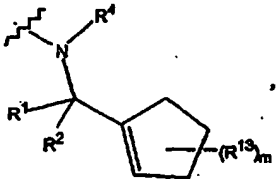
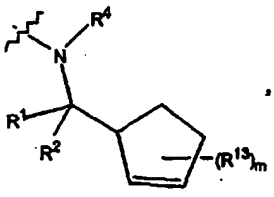
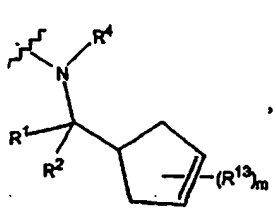
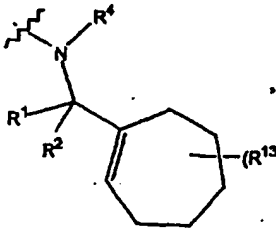
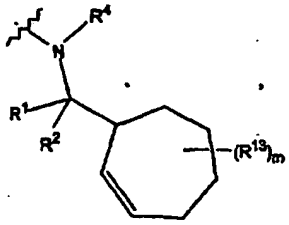
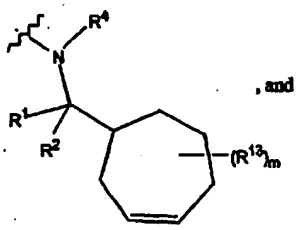


7. A compound according to any of the preceding claims of the formula 3



wherein B is selected from the group consisting of: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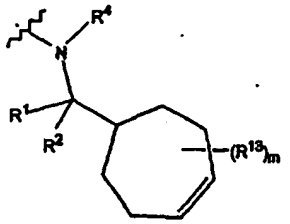
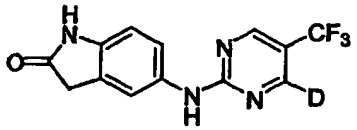
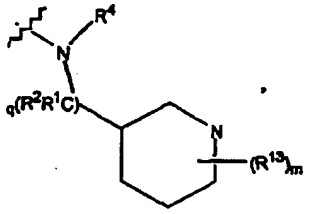
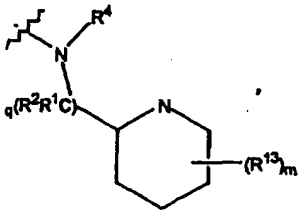
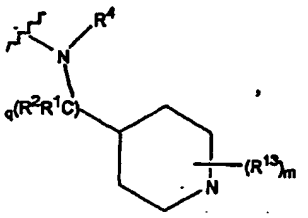
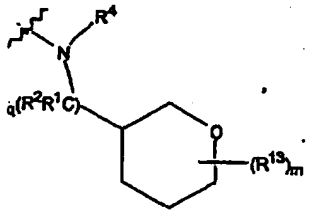
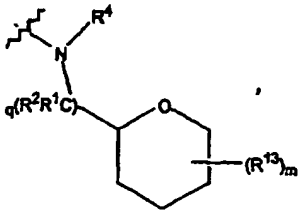
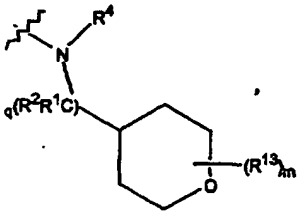
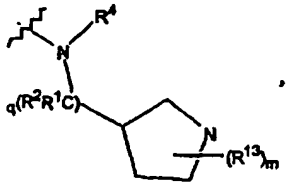
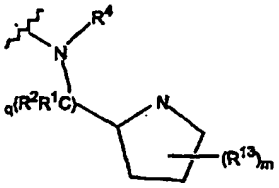
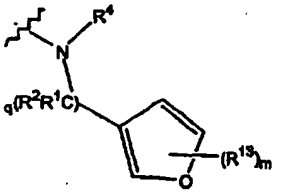
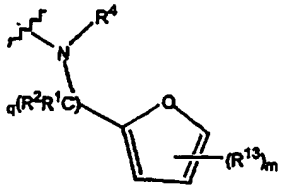
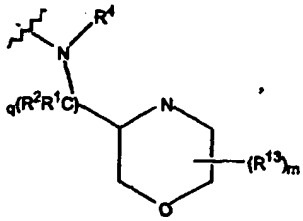
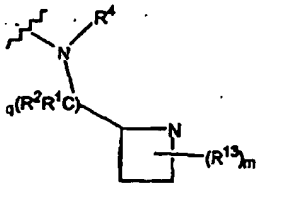


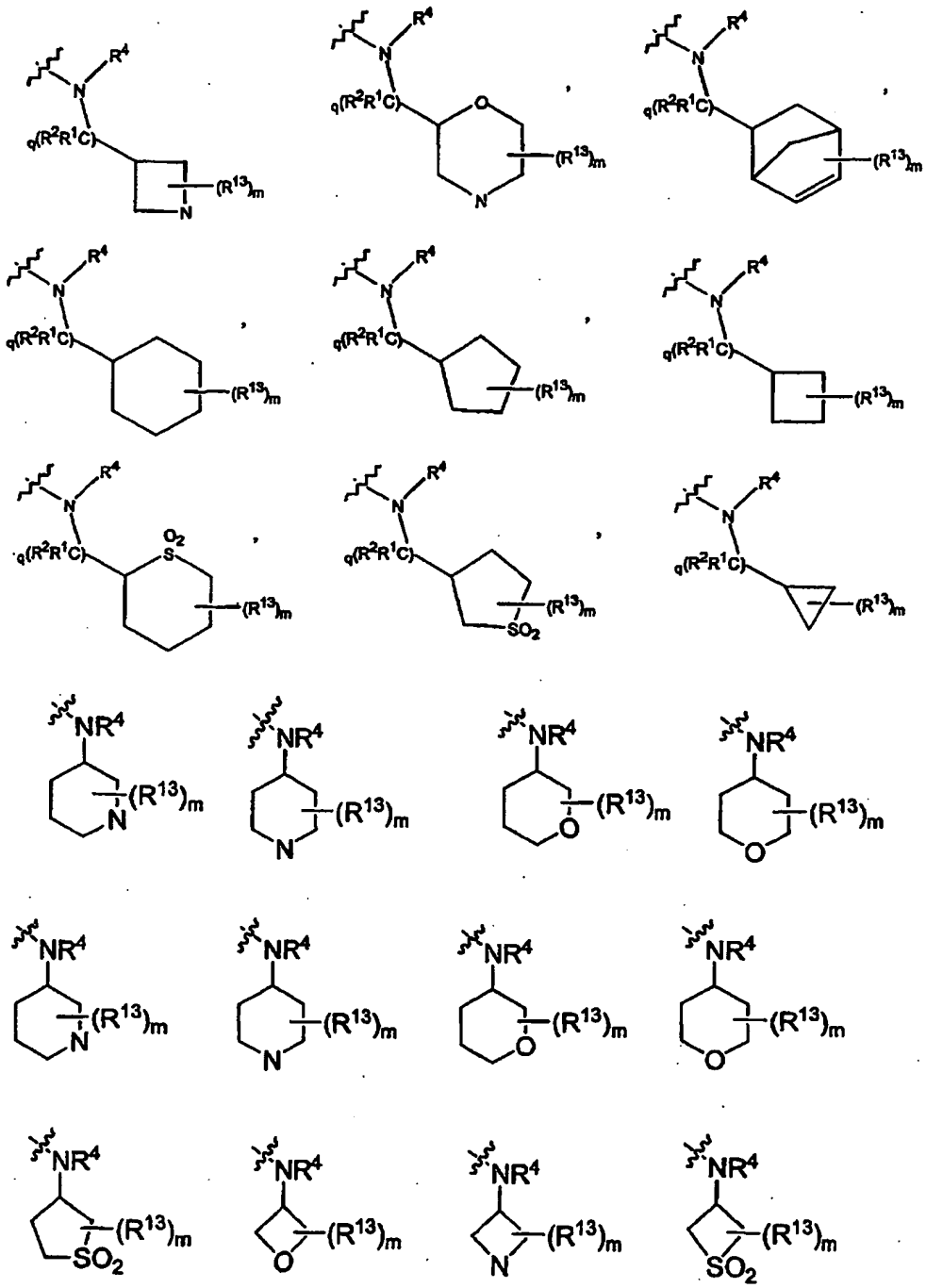
8. A compound according to any of the preceding claims of formula 4



wherein D is selected from the group consisting of:

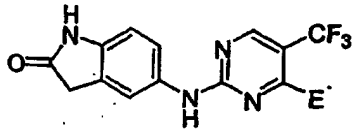













5

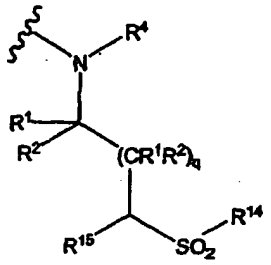


wherein q is an integer from 1-2.

9. A compound according to any of the preceding claims of formula 5:



wherein E is selected from the group consisting of:



wherein $R^{14}$ is selected from the group consisting of $(C_1-C_6)$-alkyl, $(C_3-C_7)$-cycloalkyl, and $(C_2-C_9)$-heterocyclyl, and $R^{15}$ is selected from the group consisting of hydrogen, $(C_1-C_6)$-alkyl, $(C_3-C_7)$-cycloalkyl, and $(C_2-C_9)$-heterocyclyl.

10. A compound selected from the group consisting of:

5-[4-(3-Methanesulfonyl-benzylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

Ethanesulfonic acid methyl-{3-[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-propyl}-amide;

5-{4-[(Isochroman-1-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-{4-[2-(Pyridin-3-yloxy)-propylamino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

3-{[2-(2-Oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-methyl}-benzenesulfonamide;

5-{4-[(1-Methanesulfonyl-piperidin-3-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

N-(3-{[2-(2-Oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-methyl}-phenyl)-methanesulfonamide;

N-Methyl-N-{2-[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-ethyl}-methanesulfonamide;

5-{4-[(4-Methanesulfonyl-morpholin-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-[4-(3-Methanesulfonylmethyl-benzylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-{4-[(1-Methanesulfonyl-pyrrolidin-3-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

N-Methyl-N-{3-[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-propyl}-methanesulfonamide;

5-{4-[2-(1-Methanesulfonyl-piperidin-2-yl)-ethylamino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-{4-[(4-Methanesulfonyl-pyridin-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-[4-(3-Isopropoxy-propylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-{4-[(5-Methyl-furan-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-{4-[(Bicyclo[2.2.1]hept-5-en-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

N-(4-Fluoro-3-{[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-methyl}-phenyl)-N-methyl-methanesulfonamide;

5-{4-[(1-Methanesulfonyl-piperidin-3-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-{4-[(6-Methanesulfonyl-pyridin-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-{4-[(5-Methanesulfonyl-pyridin-3-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-[4-(2-Methanesulfonyl-benzylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-{4-[(1-Pyrimidin-2-yl-piperidin-3-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-{4-[2-(1-Methanesulfonyl-piperidin-2-yl)-ethylamino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-{4-[2-(1-Methanesulfonyl-piperidin-2-yl)-ethylamino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

N-(2-{[2-(2-Oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-methyl}-phenyl)-methanesulfonamide;

5-{4-[(1-Methanesulfonyl-pyrrolidin-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

N-Methyl-N-(2-{[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-methyl}-phenyl)-methanesulfonamide;

N-Methyl-N-(2-methyl-6-{[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-methyl}-phenyl)-methanesulfonamide;

5-[4-(2-Hydroxy-indan-1-ylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-{4-[(1-Hydroxy-cyclopentylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-{4-[2-Hydroxy-2-(1-methanesulfonyl-piperidin-2-yl)-ethylamino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one; and

N-Methyl-N-(3-{[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-methyl}-pyridin-2-yl)-methanesulfonamide.

11. A method for the treatment of abnormal cell growth in a mammal comprising administering to said mammal an amount of a compound of claim 1 that is effective in treating abnormal cell growth.

12. A pharmaceutical composition for the treatment of abnormal cell growth in a mammal comprising an amount of a compound of claim 1 that is effective in treating abnormal cell growth, and a pharmaceutically acceptable carrier.

# INTERNATIONAL SEARCH REPORT

International application No
PCT/IB 03/05883

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D403/12 C07D401/14 C07D417/14 C07D413/14 C07D403/14
C07D409/14 C07D405/14 C07D513/04 A61K31/505
//(C07D403/12,239:00,209:00),(C07D401/14,239:00,211:00,209:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, EMBASE, BIOSIS, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| A,P | WO 03 032997 A (STEEGMAIER MARTIN ;KRIST BERND (AT); SPEVAK WALTER (AT); SCHOOP AN) 24 April 2003 (2003-04-24) abstract; examples 37,43 | 1-10,12 |
| A | US 5 521 184 A (ZIMMERMANN JUERG) 28 May 1996 (1996-05-28) abstract; claims | 1-10,12 |
| A | WO 97 19065 A (CELLTECH THERAPEUTICS LTD ;DAVIS PETER DAVID (GB); MOFFAT DAVID FE) 29 May 1997 (1997-05-29) abstract; claims | 1-10,12 |
| A | WO 01 60816 A (AMGEN INC) 23 August 2001 (2001-08-23) page 28; example 37 | 1-10,12 |

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 18 March 2004 | 06/04/2004 |

| Name and mailing address of the ISA | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL – 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,<br>Fax: (+31-70) 340-3016 | Frelon, D |

Form PCT/ISA/210 (second sheet) (January 2004)

# INTERNATIONAL SEARCH REPORT

International application No
PCT/IB 03/05883

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| A | WO 00 39101 A (BREAULT GLORIA ANNE ;PEASE JANET ELIZABETH (GB); ASTRAZENECA UK LT) 6 July 2000 (2000-07-06) abstract; claims | 1-10,12 |
| A | KNOCKAERT, MARIE ET AL: "Identifying in vivo targets of cyclin-dependent kinase inhibitors by affinity chromatography" BIOCHEMICAL PHARMACOLOGY ( 2002 ), 64(5-6), 819 -825 , XP002274117 the whole document | 1-10,12 |
| A | KATH J C: "PATENT FOCUS: INHIBITORS OF TUMOUR CELL GROWTH" EXPERT OPINION ON THERAPEUTIC PATENTS, ASHLEY PUBLICATIONS, GB, vol. 10, no. 6, 2000, pages 803-818, XP000919385 ISSN: 1354-3776 the whole document | 1-10,12 |
| A | STOVER D R ET AL: "RECENT ADVANCES IN PROTEIN KINASE INHIBITION: CURRENT MOLECULAR SCAFFOLDS USED FOR INHIBITOR SYNTHESIS" CURRENT OPINION IN DRUG DISCOVERY AND DEVELOPMENT, CURRENT DRUGS, LONDON, GB, vol. 2, no. 4, 1999, pages 274-285, XP000926237 ISSN: 1367-6733 the whole document | 1-10,12 |
| A | BRAMSON, H. NEAL ET AL: "Oxindole-Based Inhibitors of Cyclin-Dependent Kinase 2 (CDK2): Design, Synthesis, Enzymatic Activities, and X-ray Crystallographic Analysis" JOURNAL OF MEDICINAL CHEMISTRY (2001), 44(25), 4339-4358 , XP002274118 the whole document | 1-10,12 |

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB 03/05883

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 11 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB 03/05883

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---|---|---|
| WO 03032997 A | 24-04-2003 | WO 03032997 A1 | 24-04-2003 |
| | | US 2003171359 A1 | 11-09-2003 |
| US 5521184 A | 28-05-1996 | AT 188964 T | 15-02-2000 |
| | | AU 3569493 A | 07-10-1993 |
| | | BR 1100739 A3 | 06-06-2000 |
| | | CA 2093203 A1 | 04-10-1993 |
| | | CN 1077713 A ,B | 27-10-1993 |
| | | CY 2229 A | 18-04-2003 |
| | | CZ 9300560 A3 | 16-02-1994 |
| | | DE 59309931 D1 | 24-02-2000 |
| | | DK 564409 T3 | 19-06-2000 |
| | | EP 0564409 A1 | 06-10-1993 |
| | | ES 2142857 T3 | 01-05-2000 |
| | | FI 931458 A | 04-10-1993 |
| | | GR 3032927 T3 | 31-07-2000 |
| | | HU 64050 A2 | 29-11-1993 |
| | | IL 105264 A | 11-04-1999 |
| | | JP 2706682 B2 | 28-01-1998 |
| | | JP 6087834 A | 29-03-1994 |
| | | KR 261366 B1 | 01-08-2000 |
| | | LU 90908 A9 | 30-04-2003 |
| | | MX 9301929 A1 | 29-07-1994 |
| | | NO 931283 A | 04-10-1993 |
| | | NZ 247299 A | 26-07-1995 |
| | | PT 564409 T | 30-06-2000 |
| | | RU 2125992 C1 | 10-02-1999 |
| | | SG 43859 A1 | 14-11-1997 |
| | | SK 28093 A3 | 06-04-1994 |
| | | ZA 9302397 A | 04-10-1993 |
| | | AU 693804 B2 | 09-07-1998 |
| | | AU 7697594 A | 01-05-1995 |
| | | CA 2148477 A1 | 13-04-1995 |
| | | WO 9509852 A1 | 13-04-1995 |
| | | EP 0672040 A1 | 20-09-1995 |
| | | JP 8504834 T | 28-05-1996 |
| | | US 5543520 A | 06-08-1996 |
| WO 9719065 A | 29-05-1997 | AU 7631496 A | 11-06-1997 |
| | | DE 69627179 D1 | 08-05-2003 |
| | | DE 69627179 T2 | 29-01-2004 |
| | | EP 0862560 A1 | 09-09-1998 |
| | | ES 2195020 T3 | 01-12-2003 |
| | | WO 9719065 A1 | 29-05-1997 |
| | | US 6235746 B1 | 22-05-2001 |
| | | US 5958935 A | 28-09-1999 |
| WO 0160816 A | 23-08-2001 | AU 3704101 A | 27-08-2001 |
| | | CA 2400447 A1 | 23-08-2001 |
| | | CN 1429222 T | 09-07-2003 |
| | | EP 1257546 A1 | 20-11-2002 |
| | | HU 0301117 A2 | 29-12-2003 |
| | | JP 2003532635 T | 05-11-2003 |
| | | WO 0160816 A1 | 23-08-2001 |
| | | US 2003199534 A1 | 23-10-2003 |
| | | US 2002052386 A1 | 02-05-2002 |
| WO 0039101 A | 06-07-2000 | AU 763091 B2 | 10-07-2003 |

# INTERNATIONAL SEARCH REPORT

Information on patent family members

Internatio pplication No
PCT/IB 03/05883

| Patent document cited in search report | Publication date | Patent family member(s) | | Publication date |
|---|---|---|---|---|
| WO 0039101 A | | AU | 1874300 A | 31-07-2000 |
| | | BR | 9916590 A | 23-10-2001 |
| | | CA | 2352896 A1 | 06-07-2000 |
| | | CN | 1335838 T | 13-02-2002 |
| | | EP | 1140860 A1 | 10-10-2001 |
| | | WO | 0039101 A1 | 06-07-2000 |
| | | JP | 2002533446 T | 08-10-2002 |
| | | NO | 20013038 A | 22-08-2001 |
| | | NZ | 512118 A | 29-08-2003 |
| | | US | 6593326 B1 | 15-07-2003 |
| | | ZA | 200104413 A | 29-08-2002 |

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(75) Inventors/Applicants *(for US only)*: **KATH, John, Charles** [US/US]; Pfizer Global Research and Development, Eastern Point Road, Groton, CT 06340 (US). **LUZZIO, Michael, Joseph** [US/US]; Pfizer Global Research and Development, Eastern Point Road, Groton, CT 06340 (US).

(74) Agents: **LUMB, J., Trevor** et al.; c/o Wood, David, J., Pfizer Global Research and Development, UK Patent Department, Ramsgate Road, Sandwich, Kent CT13 9NJ (GB).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

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**Published:**
— *without international search report and to be republished upon receipt of that report*

*For two-letter codes and other abbreviations. refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

(54) Title: COMPOUNDS FOR THE TREATMENT OF ABNORMAL CELL GROWTH

(57) Abstract: The invention relates to compounds of the formula (1) and to pharmaceutically acceptable salts, prodrugs and solvates thereof, wherein $R^1$, $R^2$, $R^3$, $R^4$, $R^5$, n, A and B are as defined herein. The invention also relates to methods of treating abnormal cell growth in mammals by administering the compounds of formula (1) and to pharmaceutical compositions for treating such disorders, which contain the compounds of formula (1). The invention also relates to methods of preparing the compounds of formula (1).

WO 2004/056786 A2

# PYRIMIDINE DERIVATIVES FOR THE TREATMENT OF ABNORMAL CELL GROWTH

## Background of the Invention

This invention relates to novel pyrimidine derivatives that are useful in the treatment of abnormal cell growth, such as cancer, in mammals. This invention also relates to a method of using such compounds in the treatment of abnormal cell growth in mammals, especially humans, and to pharmaceutical compositions containing such compounds.

It is known that a cell may become cancerous by virtue of the transformation of a portion of its DNA into an oncogene (i.e., a gene which, on activation, leads to the formation of malignant tumor cells). Many oncogenes encode proteins that are aberrant tyrosine kinases capable of causing cell transformation. Alternatively, the overexpression of a normal proto-oncogenic tyrosine kinase may also result in proliferative disorders, sometimes resulting in a malignant phenotype.

Receptor tyrosine kinases are enzymes which span the cell membrane and possess an extracellular binding domain for growth factors such as epidermal growth factor, a transmembrane domain, and an intracellular portion which functions as a kinase to phosphorylate specific tyrosine residues in proteins and hence to influence cell proliferation. Other receptor tyrosine kinases include c-erbB-2, c-met, tie-2, PDGFr, FGFr, and VEGFR. It is known that such kinases are frequently aberrantly expressed in common human cancers such as breast cancer, gastrointestinal cancer such as colon, rectal or stomach cancer, leukemia, and ovarian, bronchial or pancreatic cancer. It has also been shown that epidermal growth factor receptor (EGFR), which possesses tyrosine kinase activity, is mutated and/or overexpressed in many human cancers such as brain, lung, squamous cell, bladder, gastric, breast, head and neck, oesophageal, gynecological and thyroid tumors.

Accordingly, it has been recognized that inhibitors of receptor tyrosine kinases are useful as selective inhibitors of the growth of mammalian cancer cells. For example, erbstatin, a tyrosine kinase inhibitor, selectively attenuates the growth in athymic nude mice of a transplanted human mammary carcinoma which expresses epidermal growth factor receptor tyrosine kinase (EGFR) but is without effect on the growth of another carcinoma which does not express the EGF receptor. Thus, selective inhibitors of certain receptor tyrosine kinases, are useful in the treatment of abnormal cell growth, in particular cancer, in mammals. In addition to receptor tyrosine kinses, selective inhibitors of certain non-receptor tyrosine kinases, such as FAK (focal adhesion kinase), lck, src, abl or serine/threonine kinases (e.g.: cyclin dependent kinases, are useful in the treatment of abnormal cell growth, in particular cancer, in mammals. FAK is also known as the Protein-Tyrosine Kinase 2, PTK2.

Convincing evidence suggests that FAK, a cytoplasmic, non-receptor tyrosine kinase, plays an essential role in cell-matrix signal transduction pathways (Clark and Brugge 1995, Science 268: 233-239) and its aberrant activation is associated with an increase in the

metastatic potential of tumors (Owens et al. 1995, Cancer Research 55: 2752-2755). FAK was originally identified as a 125 kDa protein highly tyrosine-phosphorylated in cells transformed by v-Src. FAK was subsequently found to be a tyrosine kinase that localizes to focal adhesions, which are contact points between cultured cells and their underlying substratum and sites of intense tyrosine phosphorylation. FAK is phosphorylated and, thus, activated in response to extracellular matrix (ECM)-binding to integrins. Recently, studies have demonstrated that an increase in FAK mRNA levels accompanied invasive transformation of tumors and attenuation of the expression of FAK (through the use of antisense oligonucleotides) induces apoptosis in tumor cells (Xu et al. 1996, Cell Growth and Diff. 7: 413-418). In addition to being expressed in most tissue types, FAK is found at elevated levels in most human cancers, particularly in highly invasive metastases.

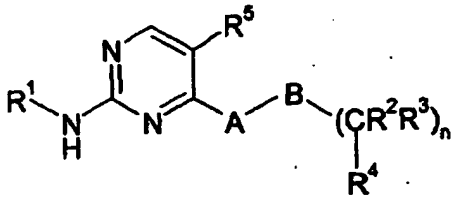
Various compounds, such as styrene derivatives, have also been shown to possess tyrosine kinase inhibitory properties. Five European patent publications, namely EP 0 566 226 A1 (published October 20, 1993), EP 0 602 851 A1 (published June 22, 1994), EP 0 635 507 A1 (published January 25, 1995), EP 0 635 498 A1 (published January 25, 1995), and EP 0 520 722 A1 (published December 30, 1992), refer to certain bicyclic derivatives, in particular quinazoline derivatives, as possessing anti-cancer properties that result from their tyrosine kinase inhibitory properties.

Also, World Patent Application WO 92/20642 (published November 26, 1992), refers to certain bis-mono and bicyclic aryl and heteroaryl compounds as tyrosine kinase inhibitors that are useful in inhibiting abnormal cell proliferation. World Patent Applications WO96/16960 (published June 6, 1996), WO 96/09294 (published March 6, 1996), WO 97/30034 (published August 21, 1997), WO 98/02434 (published January 22, 1998), WO 98/02437 (published January 22, 1998), and WO 98/02438 (published January 22, 1998), also refer to substituted bicyclic heteroaromatic derivatives as tyrosine kinase inhibitors that are useful for the same purpose.

Accordingly, a need exists for additional selective inhibitors of certain receptor and non-receptor tyrosine kinases, useful in the treatment of abnormal cell growth, such as cancer, in mammals. The present invention provides for novel pyrimidine derivatives which are selective inhibitors of the non-receptor tyrosine kinase, FAK, and are useful in the treatment of abnormal cell growth.

## Summary of the Invention

The present invention relates to a compound of the formula 1



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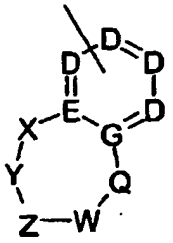
or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof,

wherein $R^1$ has the following formula 2



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wherein each D is independently selected from the group consisting of $CR^8$ and N, with the proviso that $R^1$ is linked to NH group through a ring carbon atom;

wherein E and G are independently selected from the group consisting of N and C;

wherein X, W and Q are independently selected from the group consisting of N, O, S, $SO_2$, CO, $NR^3$, $CR^2$ and $CR^2R^3$;

wherein Y and Z are independently present or absent, if present Y and Z are selected from the group consisting of N, O, S, $SO_2$, CO, $NR^3$, $CR^2$ and $CR^2R^3$;

wherein A is present or absent, if present A is selected from the group consisting of O, S and NH and wherein B is present or absent, if present B is selected from the group consisting of CO, $SO_2$, and $NR^6$, with the proviso that when A is O or S that B is absent;

wherein n is an integer from 1 to 3;

wherein each $R^2$ is independently selected from the group consisting of H, $C_1$-$C_6$ alkyl, $C_3$-$C_7$ cycloalkyl, $C_4$-$C_7$ heterocycloalkyl, $OC_1$-$C_6$ alkyl, $OC_3$-$C_7$ cycloalkyl, $OC_4$-$C_7$ heterocycloalkyl, $NH_2$, $NHR^6$, $NR^6R^7$, $SR^6$, $SOR^6$, $SO_2R^6$, $CO_2R^6$, $CONH_2$, $CONHR^6$, $CONR^6R^7$, $SO_2NH_2$, $SO_2NHR^6$, $SO_2NR^6R^7$, $NHCOR^6$, $NR^6CONR^6$, $NHCONHR^6$, $NR^6CONHR^6$, $NHCONR^6R^7$, $NR^6CONR^6R^7$, $NHSO_2R^6$, $NR^6SO_2R^6$, with the proviso that O, N or S atom of the foregoing substituents may not be bound to a carbon atom bound to another heteroatom, said alkyl, cycloalkyl, heterocycloalkyl moieties of the foregoing groups are optionally substituted by 1 to 3 substituents independently selected from the group consisting of H, halo, $C_1$-$C_6$ alkyl, CN, $NH_2$,

$NHR^{10}$, $N(R^{10})_2$, $OR^{10}$, $C_1$-$C_6$ alkyl, $C_3$-$C_7$ cycloalkyl, $C_4$-$C_7$ heterocycloalkyl, $CO_2R^{11}$, $CONH_2$, $CONHR^{11}$, and $CONR^{11}R^{12}$;

wherein each $R^3$ is independently selected from the group consisting of H, $C_1$-$C_6$ alkyl, $C_3$-$C_7$ cycloalkyl, $C_4$-$C_7$ heterocycloalkyl, $CO_2R^6$, $CONH_2$, $CONHR^6$, $CONR^6R^7$ or $R^2$ and $R^3$ taken together with the carbon atom they are linked to can form a 3-7 membered cycloalkyl ring or 4-7 membered heterocycloalkyl ring, wherein each methylene group present in said 3-7 membered cycloalkyl ring and said 4-7 membered heterocycloalkyl ring may be optionally replaced by a C=O group, said alkyl, cycloalkyl, heterocycloalkyl moieties of the foregoing groups are optionally substituted by 1 to 3 substituents independently selected from the group consisting of H, halo, $C_1$-$C_6$ alkyl, CN, $NH_2$, $NHR^{10}$, $N(R^{10})_2$, $OR^{10}$, $C_1$-$C_6$ alkyl, $C_3$-$C_7$ cycloalkyl, $C_4$-$C_7$ heterocycloalkyl, $CO_2R^{11}$, $CONH_2$, $CONHR^{11}$, and $CONR^{11}R^{12}$;

wherein $R^4$ is selected from the group consisting of H, $C_1$-$C_6$ alkyl, $C_3$-$C_7$ cycloalkyl, $C_4$-$C_7$ heterocycloalkyl, $C_6$-$C_{10}$ aryl, and 5-10 membered heteroaryl, the alkyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl moieties of the foregoing groups are optionally substituted by 1 to 3 subsitutents independently selected from the group consisting of H, halo, OH, $NO_2$, $C_1$-$C_6$ alkyl, $C(R^6)=CR^6R^7$, $C\equiv CR^6$, $C_3$-$C_7$ cycloalkyl, $C_4$-$C_7$ heterocycloalkyl, $OC_1$-$C_6$ alkyl, $OC_3$-$C_7$ cycloalkyl, $OC_4$-$C_7$ heterocycloalkyl, C=N-OH, C=N-O($C_1$-$C_6$ alkyl), $NH_2$, $NHR^6$, $NR^6R^7$, $SR^6$, $SOR^6$, $SO_2R^6$, $CO_2R^6$, $CONH_2$, $CONHR^6$, $CONR^6R^7$, $SO_2NH_2$, $SO_2NHR^6$, $SO_2NR^6R^7$, $NHCOR^6$, $NR^6CONR^6$, $NHCONHR^6$, $NR^6CONHR^6$, $NHCONR^6R^7$, $NR^6CONR^6R^7$, $NHSO_2R^6$, $NR^6SO_2R^6$, with the proviso that O, N or S atom of the foregoing substituents may not be bound to a carbon atom bound to another heteroatom;

wherein $R^5$ is selected from the group consisting of H, Br, Cl, CN, $CF_3$, $CH_2F$, $CHF_2$, $SO_2CH_3$, $CONH_2$, cyclopropyl, cyclobutyl, $C_6H_5$, $CONHR^6$, $CONR^6R^7$, $CO_2R^6$, $C(R^9)=C(R^9)_2$, and $C\equiv CR^9$;

wherein each $R^6$ is independently selected from the group consisting of H, $C_1$-$C_6$ alkyl, $C_3$-$C_7$ cycloalkyl, $C_4$-$C_7$ heterocycloalkyl, $C_6$-$C_{10}$ aryl, and 5-10 membered heteroaryl, said alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl moieties of the foregoing groups are optionally substituted by 1 to 3 substituents independently selected from the group consisting of H, halo, $C_1$-$C_6$ alkyl, CN, $NH_2$, $NHR^{10}$, $N(R^{10})_2$, $OR^{10}$, $C_1$-$C_6$ alkyl, $C_3$-$C_7$ cycloalkyl, $C_4$-$C_7$ heterocycloalkyl, $CO_2R^{11}$, $CONH_2$, $CONHR^{11}$, and $CONR^{11}R^{12}$;

wherein each $R^7$ is independently selected from the group consisting of H, $C_1$-$C_6$ alkyl, $C_3$-$C_7$ cycloalkyl, $C_4$-$C_7$ heterocycloalkyl, $C_6$-$C_{10}$ aryl, and 5-10 membered heteroaryl, said alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl moieties of the foregoing groups are optionally substituted by 1 to 3 substituents independently selected from the group consisting of H, halo, $C_1$-$C_6$ alkyl, CN, $NH_2$, $NHR^{10}$, $N(R^{10})_2$, $OR^{10}$, $C_1$-$C_6$ alkyl, $C_3$-$C_7$ cycloalkyl, $C_4$-$C_7$ heterocycloalkyl, $CO_2R^{11}$, $CONH_2$, $CONHR^{11}$, and $CONR^{11}R^{12}$;

wherein each $R^8$ is independently selected from the group consisting of H, halo, cyano, $C_1$-$C_6$ alkyl, $C_3$-$C_7$ cycloalkyl, $C_4$-$C_7$ heterocycloalkyl, $OC_1$-$C_6$ alkyl, $OC_3$-$C_7$ cycloalkyl, $OC_4$-$C_7$ heterocycloalkyl, $NH_2$, $NHR^6$, $NR^6R^7$, $SR^6$, $SOR^6$, $SO_2R^6$, $CO_2R^6$, $CONH_2$, $CONHR^6$, $CONR^6R^7$, $SO_2NH_2$, $SO_2NHR^6$, $SO_2NR^6R^7$, $NHCOR^6$, $NR^6CONR^6$, $NHCONHR^6$, $NR^6CONHR^6$, $NHCONR^6R^7$, $NR^6CONR^6R^7$, $NHSO_2R^6$, $NR^6SO_2R^6$, said alkyl, cycloalkyl, and heterocycloalkyl moieties of the foregoing groups are optionally substituted by 1 to 3 substituents independently selected from the group consisting of H, halo, $C_1$-$C_6$ alkyl, CN, $NH_2$, $NHR^3$, $N(R^3)_2$, $OR^3$, $C_1$-$C_6$ alkyl, $C_3$-$C_7$ cycloalkyl, $C_4$-$C_7$ heterocycloalkyl, $CO_2R^6$, $CONH_2$, $CONHR^6$, and $CONR^6R^7$;

wherein each $R^9$ is independently selected from the group consisting of H, $CF_3$, and $C_1$-$C_6$ alkyl, said $C_1$-$C_6$ alkyl is optionally substituted by 1 to 6 halo atoms;

wherein each $R^{10}$ is independently selected from the group consisting of H, $C_1$-$C_6$ alkyl, $C_3$-$C_7$ cycloalkyl, $C_4$-$C_7$ heterocycloalkyl, $CO_2R^{11}$, $CONH_2$, $CONHR^{11}$, $CONR^{11}R^{12}$, $SOR^{11}$, $SO_2R^{11}$, $SO_2NH_2$, $SO_2NHR^{11}$, $SO_2NR^{11}R^{12}$; said alkyl, cycloalkyl, heterocycloalkyl moieties of the foregoing groups are optionally substituted by 1 to 3 substituents independently selected from the group consisting of H, halo, $C_1$-$C_6$ alkyl, CN, $NH_2$, $NHR^{13}$, $N(R^{13})_2$, $OR^{13}$, $C_1$-$C_6$ alkyl, $C_3$-$C_7$ cycloalkyl, $C_4$-$C_7$ heterocycloalkyl, $CO_2R^{14}$, $CONH_2$, $CONHR^{14}$, and $CONR^{14}R^{15}$

wherein each $R^{11}$ is independently selected from the group consisting of H, $C_1$-$C_6$ alkyl, $C_3$-$C_7$ cycloalkyl, $C_4$-$C_7$ heterocycloalkyl, $C_6$-$C_{10}$ aryl, $C_5$-$C_{10}$ membered heteroaryl; said alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl moieties of the foregoing groups are optionally substituted by 1 to 3 substituents independently selected from the group consisting of H, halo, $C_1$-$C_6$ alkyl, CN, $NH_2$, $NHR^{13}$, $N(R^{13})_2$, $OR^{13}$, $C_1$-$C_6$ alkyl, $C_3$-$C_7$ cycloalkyl, $C_4$-$C_7$ heterocycloalkyl, $CO_2R^{14}$, $CONH_2$, $CONHR^{14}$, and $CONR^{14}R^{15}$;

wherein each $R^{12}$ is independently selected from the group consisting of H, $C_1$-$C_6$ alkyl, $C_3$-$C_7$ cycloalkyl, $C_4$-$C_7$ heterocycloalkyl, $C_6$-$C_{10}$ aryl, $C_5$-$C_{10}$ membered heteroaryl; said alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl moieties of the foregoing groups are optionally substituted by 1 to 3 substituents independently selected from the group consisting of H, halo, $C_1$-$C_6$ alkyl, CN, $NH_2$, $NHR^{13}$, $N(R^{13})_2$, $OR^{13}$, $C_1$-$C_6$ alkyl, $C_3$-$C_7$ cycloalkyl, $C_4$-$C_7$ heterocycloalkyl, $CO_2R^{14}$, $CONH_2$, $CONHR^{14}$, and $CONR^{14}R^{15}$;

wherein each $R^{13}$ is independently selected from the group consisting of H, $C_1$-$C_6$ alkyl, $C_3$-$C_7$ cycloalkyl, $C_4$-$C_7$ heterocycloalkyl, $CO_2R^{14}$, $CONH_2$, $CONHR^{14}$, $CONR^{14}R^{15}$, $SOR^{14}$, $SO_2R^{14}$, $SO_2NH_2$, $SO_2NHR^{14}$, $SO_2NR^{14}R^{15}$;

wherein each $R^{14}$ is independently selected from the group consisting of H, $C_1$-$C_6$ alkyl, $C_3$-$C_7$ cycloalkyl, $C_4$-$C_7$ heterocycloalkyl, $C_6$-$C_{10}$ aryl, $C_5$-$C_{10}$ membered heteroaryl; said alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl moieties of the foregoing groups are optionally substituted by 1 to 3 substituents independently selected from the group consisting of H, halo, $C_1$-$C_6$ alkyl, CN, $NH_2$, NH $C_1$-$C_6$alkyl, $N(C_1$-$C_6$alkyl$)_2$, O-$C_1$-$C_6$ alkyl; and

wherein each $R^{15}$ is independently selected from the group consisting of H, $C_1$-$C_6$ alkyl, $C_3$-$C_7$ cycloalkyl, $C_4$-$C_7$ heterocycloalkyl, $C_6$-$C_{10}$ aryl, $C_5$-$C_{10}$ membered heteroaryl; said alkyl,

cycloalkyl, heterocycloalkyl, aryl, and heteroaryl moieties of the foregoing groups are optionally substituted by 1 to 3 substituents independently selected from the group consisting of H, halo, $C_1$-$C_6$ alkyl, CN, $NH_2$, NH $C_1$-$C_6$alkyl, N($C_1$-$C_6$alkyl)$_2$, O-$C_1$-$C_6$ alkyl.

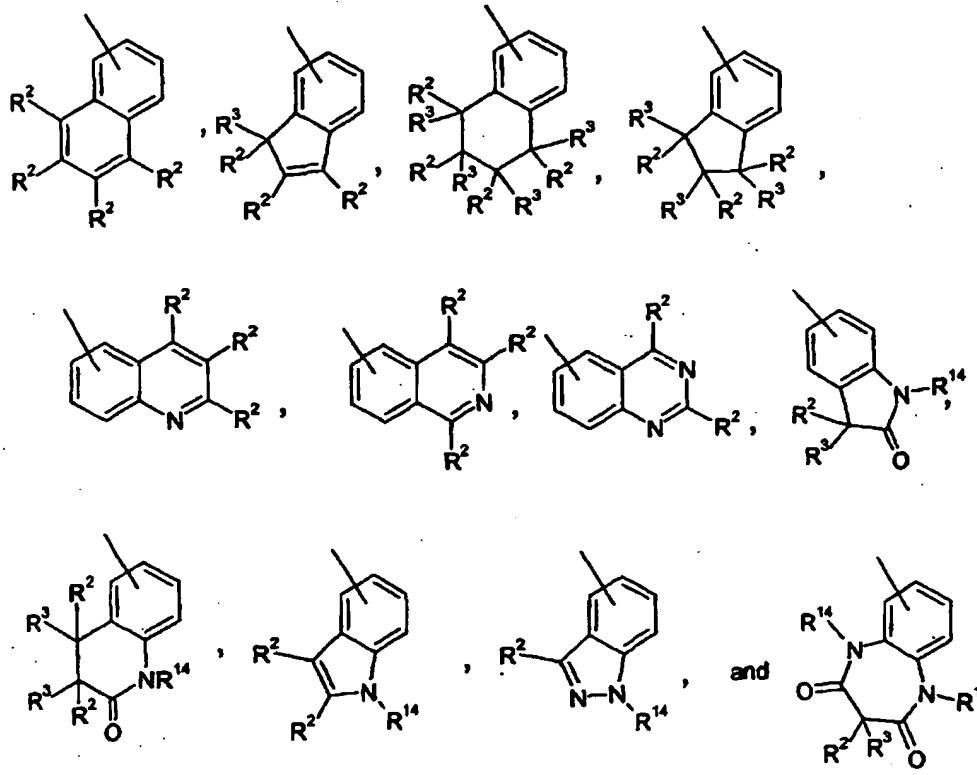
In one preferred embodiment of the compounds of formula 1, include those wherein E and G are independently selected from the group consisting of N and C; wherein X, W and Q are independently selected from the group consisting of N, O, CO, $NR^3$, $CR^2$ and $CR^2R^3$; and wherein Y and Z are independently present or absent, if present Y and Z are selected from the group consisting of N, O, CO, $NR^3$, $CR^2$ and $CR^2R^3$.

In another preferred embodiment of the compounds of formula 1, include those wherein E and G are independently selected from the group consisting of N and C; wherein X, W and Q are independently selected from the group consisting of N, CO, $NR^3$, $CR^2$ and $CR^2R^3$; and wherein Y and Z are independently present or absent, if present Y and Z are selected from the group consisting of N, CO, $NR^3$, $CR^2$ and $CR^2R^3$.

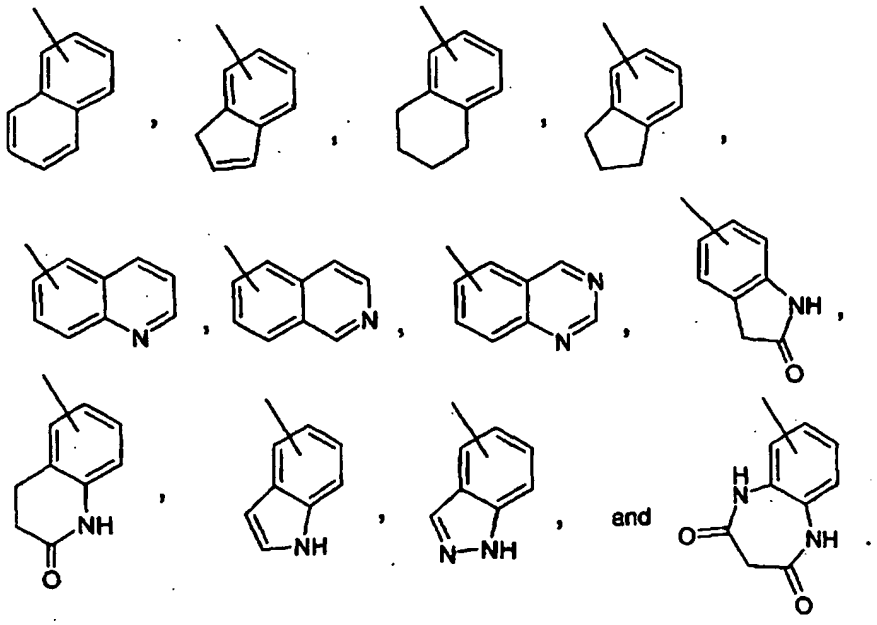
In a more preferred embodiment of the compounds of formula 1, include those wherein E and G are C; wherein X, W and Q are independently selected from the group consisting of N, CO, $NR^3$, $CR^2$ and $CR^2R^3$; and wherein Y and Z are independently present or absent, if present Y and Z are selected from the group consisting of N, CO, $NR^3$, $CR^2$ and $CR^2R^3$.

In a most preferred embodiment of the compounds of formula 1, include those wherein E and G are C; wherein X, W and Q are independently selected from the group consisting of N, $NR^3$, $CR^2$ and $CR^2R^3$; and wherein Y and Z are independently present or absent, if present Y and Z are selected from the group consisting of N, $NR^3$, $CR^2$ and $CR^2R^3$.

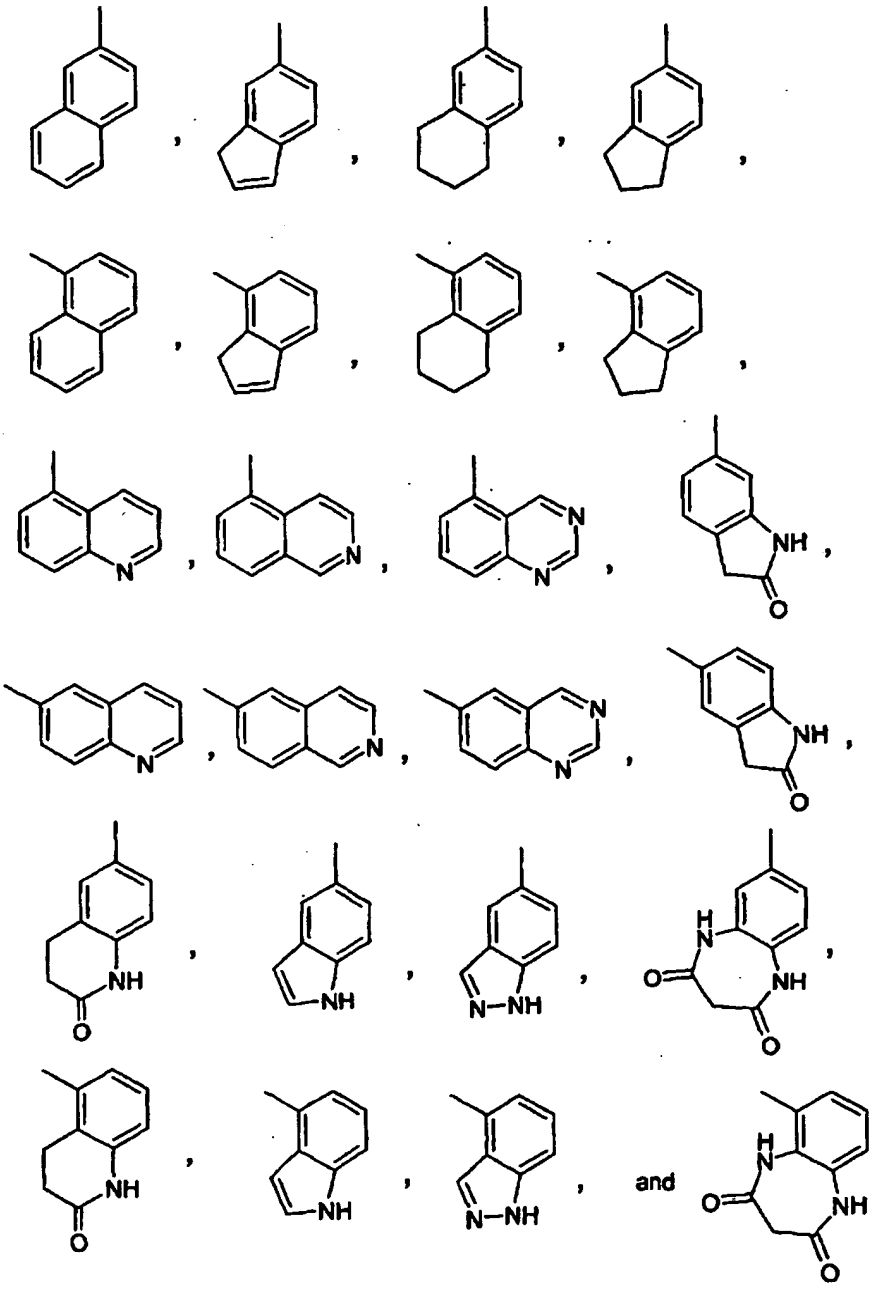
In one specific embodiment of the compounds of formula 1, include those wherein $R^2$ is selected from the group consisting of:



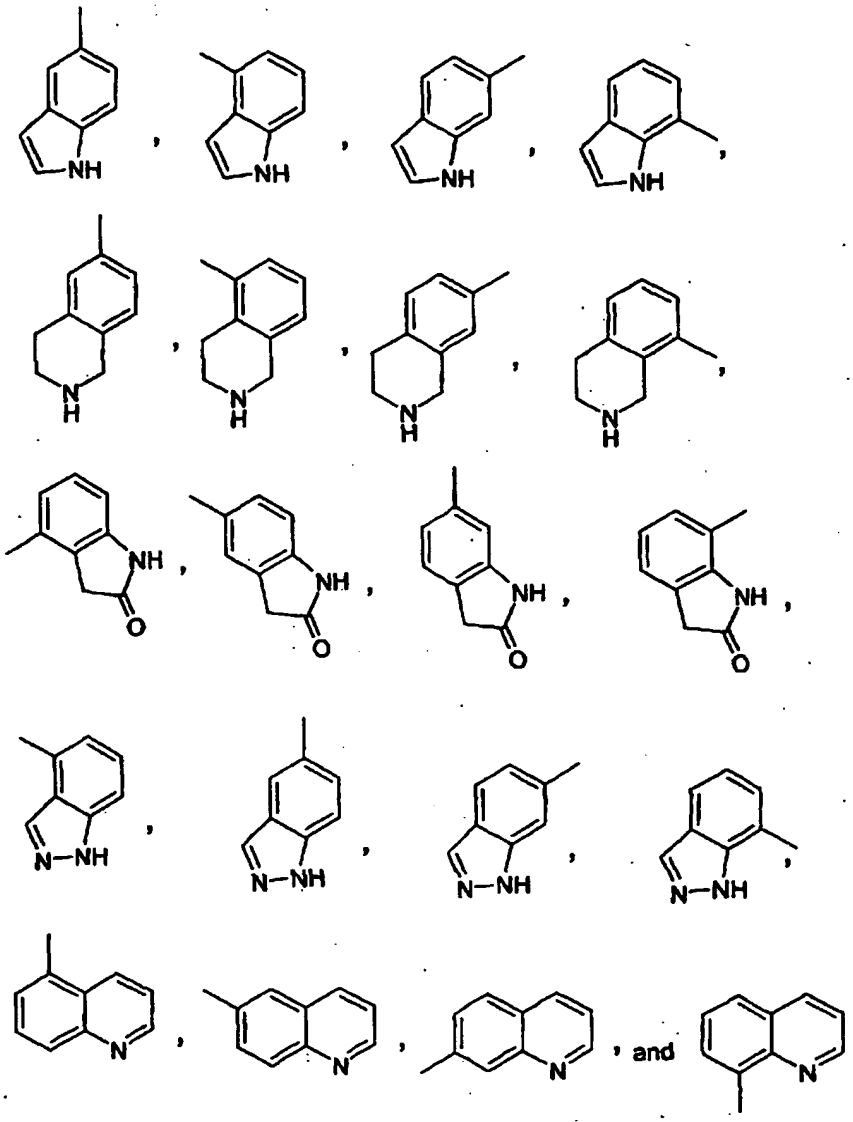
In another specific embodiment of the compounds of formula 1, include those wherein $R^2$ is selected from the group consisting of:



In another specific embodiment of the compounds of formula 1, include those wherein $R^2$ is selected from the group consisting of:



Specific embodiments of the compounds of formula 1 include those wherein $R^2$ is selected from the group consisting of:



Specific embodiments of the compounds of formula 1 include those wherein A is present or absent, if present A is selected from the group consisting of O and NH and wherein B is present or absent, if present B is selected from the group consisting of CO, $SO_2$, and $NR^6$, with the proviso that when A is O that B is absent.

Specific embodiments of the compounds of formula 1 include those wherein A is present or absent, if present A is NH and wherein B is present or absent, if present B is selected from the group consisting of CO, $SO_2$, and $NR^6$.

Specific embodiments of the compounds of formula 1 include those wherein A is present or absent, if present A is NH and wherein B is present or absent, if present B is selected from the group consisting of CO and $NR^6$.

In one preferred embodiment of the compounds of formula 1 include those wherein A is present or absent, if present A is NH and wherein B is present or absent, if present B is CO.

In a more preferred embodiment of the compounds of formula 1 include those wherein A is present or absent, if present A is NH and wherein B is absent.

In a most preferred embodiment of the compounds of formula 1 include those wherein A is NH and wherein B is absent.

Specific embodiments of the compounds of formula 1 include those each $R^2$ is independently selected from the group consisting of H, $C_1$-$C_6$ alkyl, $C_3$-$C_7$ cycloalkyl, $C_4$-$C_7$ heterocycloalkyl, $OC_1$-$C_6$ alkyl, $OC_3$-$C_7$ cycloalkyl, $OC_4$-$C_7$ heterocycloalkyl, $NH_2$, $NHR^6$, $NR^6R^7$, $SR^6$, $SOR^6$, $SO_2R^6$, $CO_2R^6$, $CONH_2$, $CONHR^6$, $CONR^6R^7$, $NHCOR^6$, $NR^6CONR^6$, $NHCONHR^6$, $NR^6CONHR^6$, $NHCONR^6R^7$, $NR^6CONR^6R^7$, $NHSO_2R^6$, $NR^6SO_2R^6$, with the proviso that O, N or S atom of the foregoing substituents may not be bound to a carbon atom bound to another heteroatom, said alkyl, cycloalkyl, heterocycloalkyl moieties of the foregoing groups are optionally substituted by 1 to 3 substituents independently selected from the group consisting of H, halo, $C_1$-$C_6$ alkyl, CN, $NH_2$, $NHR^{10}$, $N(R^{10})_2$, $OR^{10}$, $C_1$-$C_6$ alkyl, $C_3$-$C_7$ cycloalkyl, $C_4$-$C_7$ heterocycloalkyl, $CO_2R^{11}$, $CONH_2$, $CONHR^{11}$, and $CONR^{11}R^{12}$ ; and wherein each $R^3$ is independently selected from the group consisting of H, $C_1$-$C_6$ alkyl, $C_3$-$C_7$ cycloalkyl, $C_4$-$C_7$ heterocycloalkyl, $CO_2R^6$, $CONH_2$, $CONHR^6$, $CONR^6R^7$ or $R^2$ and $R^3$ taken together with the carbon atom they are linked to can form a 3-7 membered cycloalkyl ring or 4-7 membered heterocycloalkyl ring, wherein each methylene group present in said 3-7 membered cycloalkyl ring and said 4-7 membered heterocycloalkyl ring may be optionally replaced by a C=O group, said alkyl, cycloalkyl, heterocycloalkyl moieties of the foregoing groups are optionally substituted by 1 to 3 substituents independently selected from the group consisting of H, halo, $C_1$-$C_6$ alkyl, CN, $NH_2$, $NHR^{10}$, $N(R^{10})_2$, $OR^{10}$, $C_1$-$C_6$ alkyl, $C_3$-$C_7$ cycloalkyl, $C_4$-$C_7$ heterocycloalkyl, $CO_2R^{11}$, $CONH_2$, $CONHR^{11}$, and $CONR^{11}R^{12}$ .

Specific embodiments of the compounds of formula 1 include those each $R^2$ is independently selected from the group consisting of H, $C_1$-$C_6$ alkyl, $C_3$-$C_7$ cycloalkyl, $C_4$-$C_7$ heterocycloalkyl, $OC_1$-$C_6$ alkyl, $OC_3$-$C_7$ cycloalkyl, $OC_4$-$C_7$ heterocycloalkyl, $NH_2$, $NHR^6$, $NR^6R^7$, with the proviso that O, N or S atom of the foregoing substituents may not be bound to a carbon atom bound to another heteroatom, said alkyl, cycloalkyl, heterocycloalkyl moieties of the foregoing groups are optionally substituted by 1 to 3 substituents independently selected from the group consisting of H, halo, $C_1$-$C_6$ alkyl, CN, $NH_2$, $NHR^{10}$, $N(R^{10})_2$, $OR^{10}$, $C_1$-$C_6$ alkyl, $C_3$-$C_7$ cycloalkyl, $C_4$-$C_7$ heterocycloalkyl, $CO_2R^{11}$, $CONH_2$, $CONHR^{11}$, and $CONR^{11}R^{12}$ ; and wherein each $R^3$ is independently selected from the group consisting of H, $C_1$-$C_6$ alkyl, $C_3$-$C_7$ cycloalkyl,

$C_4$-$C_7$ heterocycloalkyl, $CO_2R^6$, $CONH_2$, $CONHR^6$, $CONR^6R^7$ or $R^2$ and $R^3$ taken together with the carbon atom they are linked to can form a 3-7 membered cycloalkyl ring or 4-7 membered heterocycloalkyl ring, wherein each methylene group present in said 3-7 membered cycloalkyl ring and said 4-7 membered heterocycloalkyl ring may be optionally replaced by a C=O group, said alkyl, cycloalkyl, heterocycloalkyl moieties of the foregoing groups are optionally substituted by 1 to 3 substituents independently selected from the group consisting of H, halo, $C_1$-$C_6$ alkyl, CN, $NH_2$, $NHR^{10}$, $N(R^{10})_2$, $OR^{10}$, $C_1$-$C_6$ alkyl, $C_3$-$C_7$ cycloalkyl, $C_4$-$C_7$ heterocycloalkyl, $CO_2R^{11}$, $CONH_2$, $CONHR^{11}$, and $CONR^{11}R^{12}$.

Specific embodiments of the compounds of formula 1 include those $R^4$ is selected from the group consisting of H, $C_1$-$C_6$ alkyl, $C_6$-$C_{10}$ aryl, and 5-10 membered heteroaryl, the alkyl, aryl and heteroaryl moieties of the foregoing groups are optionally substituted by 1 to 3 subsitutents independently selected from the group consisting of H, halo, OH, $NO_2$, $C_1$-$C_6$ alkyl, $C(R^6)=CR^6R^7$, $C\equiv CR^6$, $C_3$-$C_7$ cycloalkyl, $C_4$-$C_7$ heterocycloalkyl, $OC_1$-$C_6$ alkyl, $OC_3$-$C_7$ cycloalkyl, $OC_4$-$C_7$ heterocycloalkyl, C=N-OH, C=N-O($C_1$-$C_6$ alkyl), $NH_2$, $NHR^6$, $NR^6R^7$, $SR^6$, $SOR^6$, $SO_2R^6$, $CO_2R^6$, $CONH_2$, $CONHR^6$, $CONR^6R^7$, $SO_2NH_2$, $SO_2NHR^6$, $SO_2NR^6R^7$, $NHCOR^6$, $NR^6CONR^6$, $NHCONHR^6$, $NR^6CONHR^6$, $NHCONR^6R^7$, $NR^6CONR^6R^7$, $NHSO_2R^6$, $NR^6SO_2R^6$, with the proviso that O, N or S atom of the foregoing substituents may not be bound to a carbon atom bound to another heteroatom.

Specific embodiments of the compounds of formula 1 include those $R^4$ is selected from the group consisting of H, $C_1$-$C_6$ alkyl, and $C_6$-$C_{10}$ aryl, wherein the alkyl, and aryl moieties of the foregoing groups are optionally substituted by 1 to 3 subsitutents independently selected from the group consisting of H, halo, OH, $NO_2$, $C_1$-$C_6$ alkyl, $C(R^6)=CR^6R^7$, $C\equiv CR^6$, $C_3$-$C_7$ cycloalkyl, $C_4$-$C_7$ heterocycloalkyl, $OC_1$-$C_6$ alkyl, $OC_3$-$C_7$ cycloalkyl, $OC_4$-$C_7$ heterocycloalkyl, C=N-OH, C=N-O($C_1$-$C_6$ alkyl), $NH_2$, $NHR^6$, $NR^6R^7$, $SR^6$, $SOR^6$, $SO_2R^6$, $CO_2R^6$, $CONH_2$, $CONHR^6$, $CONR^6R^7$, $SO_2NH_2$, $SO_2NHR^6$, $SO_2NR^6R^7$, $NHCOR^6$, $NR^6CONR^6$, $NHCONHR^6$, $NR^6CONHR^6$, $NHCONR^6R^7$, $NR^6CONR^6R^7$, $NHSO_2R^6$, $NR^6SO_2R^6$, with the proviso that O, N or S atom of the foregoing substituents may not be bound to a carbon atom bound to another heteroatom.

Specific embodiments of the compounds of formula 1 include those $R^5$ is selected from the group consisting of H, Br, Cl, CN, $CF_3$, $CH_2F$, $CHF_2$, $SO_2CH_3$, $CONH_2$, $C_6H_5$, $CONHR^6$, $CONR^6R^7$, $CO_2R^6$, $C(R^9)=C(R^9)_2$, and $C\equiv CR^9$.

Specific embodiments of the compounds of formula 1 include those $R^5$ is selected from the group consisting of H, Br, Cl, CN, $CF_3$, $CH_2F$, $CHF_2$, $SO_2CH_3$, $CONH_2$, and $C_6H_5$.

Specific embodiments of the compounds of formula 1 include those $R^5$ is selected from the group consisting of H, Br, Cl, CN, $CF_3$, $CH_2F$, $CHF_2$, $SO_2CH_3$, and $CONH_2$.

Other specific embodiments of the compounds of formula 1 include those selected from the group consisting of:

5-Bromo-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-$N^4$-p-tolyl-pyrimidine-2,4-diamine;

5-Bromo-$N^4$-pyridin-2-yl-N2-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine;

5-Bromo-$N^4$-pyridin-2-ylmethyl-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine;

$N^4$-Benzyl-5-bromo-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine;

5-Bromo-N4-(1R-phenyl-ethyl)-N2-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine;

5-Bromo-$N^4$-(1rac-phenyl-ethyl)-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine;

5-Bromo-N4-(1S-phenyl-ethyl)-N2-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine;

4-({5-Bromo-2-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-ylamino]-pyrimidin-4-ylamino)-methyl)-benzenesulfonamide

5-Bromo-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-$N^4$-(4-trifluoromethyl-benzyl)-pyrimidine-2,4-diamine;

5-Bromo-$N^4$-(4-methoxy-benzyl)-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine;

5-Bromo-$N^4$-(4-fluoro-benzyl)-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine;

5-Bromo-$N^4$-(3-fluoro-benzyl)-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine;

5-Bromo-$N^4$-naphthalen-1-ylmethyl-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine;

5-Bromo-$N^4$-(4-fluoro-3-trifluoromethyl-benzyl)-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine;

5-Bromo-$N^4$-(3-fluoro-5-trifluoromethyl-benzyl)-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine;

5-Bromo-$N^4$-(4-phenoxy-benzyl)-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine;

5-Bromo-$N^4$-(3,4-difluoro-benzyl)-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine;

5-Bromo-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-$N^4$-(3-trifluoromethoxy-benzyl)-pyrimidine-2,4-diamine;

5-Bromo-$N^4$-(4-chloro-benzyl)-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine;

5-Bromo-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-$N^4$-thiophen-2-ylmethyl-pyrimidine-2,4-diamine;

5-Bromo-N4-furan-2-ylmethyl-N2-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine;

5-Bromo-$N^4$-(2-methyl-benzyl)-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine;

5-Bromo-$N^4$-(3-methyl-benzyl)-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine;

5-Bromo-$N^4$-(4-methyl-benzyl)-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine;

5-Bromo-$N^4$-(2-fluoro-benzyl)-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine;

$N^4$-Biphenyl-2-ylmethyl-5-bromo-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine;

$N^4$-Biphenyl-3-ylmethyl-5-bromo-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine;

5-Bromo-$N^4$-(2-methoxy-benzyl)-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine;

5-Bromo-$N^4$-(3-methoxy-benzyl)-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine;

3-({5-Bromo-2-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-ylamino]-pyrimidin-4-ylamino}-methyl)-N-methyl-benzamide

5-Bromo-$N^4$-(2-chloro-benzyl)-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine;

5-Bromo-$N^4$-phenethyl-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine;

5-Bromo-$N^4$-(2-pyridin-2-yl-ethyl)-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine;

5-Bromo-$N^4$-(2-pyridin-4-yl-ethyl)-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine;

5-Bromo-$N^4$-(2-pyridin-3-yl-ethyl)-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine;

5-Bromo-$N^4$-[2-(3-fluoro-phenyl)-ethyl]-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine;

5-Bromo-$N^4$-(2-phenyl-cyclopropyl)-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine;

5-Bromo-$N^4$-(2-phenyl-cyclopropyl)-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine; (homo-chiral)

5-Bromo-$N^4$-(2-phenyl-cyclopropyl)-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine; (homo-chiral)

5-Bromo-$N^4$-[2-(4-chloro-phenyl)-ethyl]-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine;

5-Bromo-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-$N^4$-(2-thiophen-2-yl-ethyl)-pyrimidine-2,4-diamine;

5-Bromo-$N^4$-[2-(2-fluoro-phenyl)-ethyl]-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine;

5-Bromo-$N^4$-[2-(2-chloro-phenyl)-ethyl]-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine;

5-Bromo-$N^4$-[2-(2-methoxy-phenyl)-ethyl]-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine;

$N^4$-(2-Benzo[1,3]dioxol-5-yl-ethyl)-5-bromo-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine;

5-Bromo-$N^4$-(3-phenyl-propyl)-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine;

5-(5-Bromo-4-phenethylamino-pyrimidin-2-ylamino)-1,3-dihydro-indol-2-one;

5-[5-Bromo-4-(2-chloro-benzylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-(4-Benzylamino-5-bromo-pyrimidin-2-ylamino)-1,3-dihydro-indol-2-one;

5-[5-Bromo-4-(1-phenyl-ethylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-[5-Bromo-4-(3-phenyl-propylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-Bromo-$N^4$-(2-methanesulfonyl-ethyl)-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine;

$N^4$-Benzyl-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine;

$N^4$-Benzyl-$N^4$-methyl-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine;

$N^4$-Methyl-$N^4$-(2-pyridin-2-yl-ethyl)-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine;

[4-(2-Phenyl-morpholin-4-yl)-pyrimidin-2-yl]-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-amine

5-Methyl-$N^4$-(2-pyridin-2-yl-ethyl)-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine;

5-Bromo-$N^2$-(3-piperidin-4-yl-1H-indol-5-yl)-$N^4$-(2-pyridin-2-yl-ethyl)-pyrimidine-2,4-diamine;

5-Bromo-$N^2$-[1-methanesulfonyl-3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-$N^4$-(2-pyridin-2-yl-ethyl)-pyrimidine-2,4-diamine;

5-Bromo-$N^2$-[1-methanesulfonyl-3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-$N^4$-pyridin-2-yl-pyrimidine-2,4-diamine;

5-Bromo-$N^2$-(2-pyridin-2-yl-ethyl)-$N^4$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine;

3-{4-(2-Pyridin-2-yl-ethylamino)-2-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-ylamino]-pyrimidin-5-yl}-acrylic acid; ethyl ester;

5-{5-Bromo-4-[2-(3-chloro-phenyl)-ethylamino]-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-Bromo-$N^4$-[2-(3-chloro-phenyl)-ethyl]-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine;

5-Bromo-$N^4$-[2-(3-chloro-phenyl)-ethyl]-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine;

5-{5-Bromo-4-[2-(4-methoxy-phenyl)-ethylamino]-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-Bromo-$N^4$-[2-(4-methoxy-phenyl)-ethyl]-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine;

5-{5-Bromo-4-[2-(3-methoxy-phenyl)-ethylamino]-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-Bromo-$N^4$-[2-(3-methoxy-phenyl)-ethyl]-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine;

5-[5-Bromo-4-(2-o-tolyl-ethylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-Bromo-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-$N^4$-(2-o-tolyl-ethyl)-pyrimidine-2,4-diamine;

5-[5-Bromo-4-(2-m-tolyl-ethylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-Bromo-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-$N^4$-(2-m-tolyl-ethyl)-pyrimidine-2,4-diamine;

5-[5-Bromo-4-(2-p-tolyl-ethylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-Bromo-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-$N^4$-(2-p-tolyl-ethyl)-pyrimidine-2,4-diamine;

[5-Bromo-2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-pyrimidin-4-ylamino]-acetic acid;

5-{5-Bromo-4-[2-(3-trifluoromethyl-phenyl)-ethylamino]-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-[4-(2-Biphenyl-4-yl-ethylamino)-5-bromo-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-{5-Bromo-4-[2-(3-fluoro-phenyl)-ethylamino]-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-{5-Bromo-4-[2-(2-chloro-phenyl)-ethylamino]-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-{5-Bromo-4-[2-(2-methoxy-phenyl)-ethylamino]-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-{5-Bromo-4-[2-(4-fluoro-phenyl)-ethylamino]-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-{5-Bromo-4-[2-(4-chloro-phenyl)-ethylamino]-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-{5-Bromo-4-[2-(2-fluoro-phenyl)-ethylamino]-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-[5-Bromo-4-(3-phenyl-allylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-{5-Bromo-4-[(thiophen-2-ylmethyl)-amino]-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

6-{5-Bromo-4-[(thiophen-2-ylmethyl)-amino]-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-[5-Bromo-4-(2,3-dimethyl-benzylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

6-[5-Bromo-4-(2,3-dimethyl-benzylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-[5-Bromo-4-(2,5-dimethyl-benzylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

6-[5-Bromo-4-(2,5-dimethyl-benzylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

6-[5-Bromo-4-(2-fluoro-benzylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

6-[5-Bromo-4-(2-trifluoromethoxy-benzylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-[5-Bromo-4-(3-trifluoromethoxy-benzylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

6-[5-Bromo-4-(3-trifluoromethoxy-benzylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-[5-Bromo-4-(4-trifluoromethoxy-benzylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

6-[5-Bromo-4-(4-trifluoromethoxy-benzylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

6-[5-Bromo-4-(2-methoxy-benzylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

6-[5-Bromo-4-(3-methoxy-benzylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

6-[5-Bromo-4-(3-trifluoromethyl-benzylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-[5-Bromo-4-[(thiazol-2-ylmethyl)-amino]-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-{5-Bromo-4-[(5-methanesulfonyl-thiophen-2-ylmethyl)-amino}-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-[5-Bromo-4-(2,3-difluoro-benzylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

6-[5-Bromo-4-(2,3-difluoro-benzylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-[5-Bromo-4-(2,4-difluoro-benzylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

6-[5-Bromo-4-(2,4-difluoro-benzylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

6-[5-Chloro-4-(2-trifluoromethyl-benzylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-Chloro-N2-(1-methyl-1H-indol-5-yl)-N4-(2-trifluoromethyl-benzyl)-pyrimidine-2,4-diamine;

5-Chloro-$N^2$-(1H-indazol-5-yl)-$N^4$-(2-trifluoromethyl-benzyl)-pyrimidine-2,4-diamine;

5-Chloro-$N^2$-(1-methyl-1H-indol-5-yl)-$N^4$-pyridin-2-ylmethyl-pyrimidine-2,4-diamine;

6-{5-Chloro-4-[(pyridin-2-ylmethyl)-amino]-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-Chloro-N2-(1H-indazol-6-yl)-N4-(2-trifluoromethyl-benzyl)-pyrimidine-2,4-diamine;

5-Chloro-N2-(1H-indazol-6-yl)-N4-pyridin-2-ylmethyl-pyrimidine-2,4-diamine;

(5-{5-Bromo-4-[(pyridin-2-ylmethyl)-amino]-pyrimidin-2-ylamino}-indazol-1-yl)-acetic acid; tert-butyl ester;

(6-{5-Bromo-4-[(pyridin-2-ylmethyl)-amino]-pyrimidin-2-ylamino}-indazol-2-yl)-acetic acid; tert-butyl ester;

6-{4-[(Pyridin-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

N2-(1-Methyl-1H-indol-5-yl)-N4-pyridin-2-ylmethyl-5-trifluoromethyl-pyrimidine-2,4-diamine;

(6-{5-Bromo-4-[(pyridin-2-ylmethyl)-amino]-pyrimidin-2-ylamino}-indol-1-yl)-acetic acid; tert-butyl ester;

N4-Pyridin-2-ylmethyl-N2-quinolin-5-yl-5-trifluoromethyl-pyrimidine-2,4-diamine;

2-(6-{5-Bromo-4-[(pyridin-2-ylmethyl)-amino]-pyrimidin-2-ylamino}-indol-1-yl)-N-(2-methoxy-ethyl)-acetamide;

6-{5-Chloro-4-[(3-methyl-pyridin-2-ylmethyl)-amino]-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

(6-{5-Bromo-4-[(pyridin-2-ylmethyl)-amino]-pyrimidin-2-ylamino}-indol-1-yl)-acetic acid;

(6-{5-Bromo-4-[(pyridin-2-ylmethyl)-amino]-pyrimidin-2-ylamino}-indazol-1-yl)-acetic acid; tert-butyl ester;

N2-(1H-Indazol-6-yl)-N4-pyridin-2-ylmethyl-5-trifluoromethyl-pyrimidine-2,4-diamine;

(5-{5-Bromo-4-[(pyridin-2-ylmethyl)-amino]-pyrimidin-2-ylamino}-indol-1-yl)-acetic acid; tert-butyl ester;

(6-{5-Bromo-4-[(pyridin-2-ylmethyl)-amino]-pyrimidin-2-ylamino}-indazol-1-yl)-acetic acid;

(5-{5-Bromo-4-[(pyridin-2-ylmethyl)-amino]-pyrimidin-2-ylamino}-indol-1-yl)-acetic acid;

(5-{5-Bromo-4-[(pyridin-2-ylmethyl)-amino]-pyrimidin-2-ylamino}-indazol-1-yl)-acetic acid;

5-{5-Chloro-4-[(3-methyl-pyridin-2-ylmethyl)-amino]-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-[5-Chloro-4-(3-methanesulfonyl-benzylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

6-[5-Chloro-4-(3-methyl-benzylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-[5-Chloro-4-(2-fluoro-benzylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

6-[5-Chloro-4-(2-fluoro-benzylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-[5-Bromo-4-(2-methoxy-ethylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-[5-Chloro-4-(3-methyl-benzylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

6-{5-Chloro-4-[(4-methyl-pyridin-2-ylmethyl)-amino]-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-(4-Benzylamino-5-chloro-pyrimidin-2-ylamino)-1,3-dihydro-indol-2-one;

5-Bromo-N2-(1H-indol-5-yl)-N4-pyridin-2-ylmethyl-pyrimidine-2,4-diamine;

5-Bromo-N2-(1H-indol-5-yl)-N4-(2-pyridin-2-yl-ethyl)-pyrimidine-2,4-diamine;

5-Bromo-N2-(1H-indol-4-yl)-N4-(2-pyridin-2-yl-ethyl)-pyrimidine-2,4-diamine;

5-Bromo-N2-(1H-indazol-5-yl)-N4-(2-pyridin-2-yl-ethyl)-pyrimidine-2,4-diamine;

5-Bromo-N2-(1H-indazol-6-yl)-N4-(2-pyridin-2-yl-ethyl)-pyrimidine-2,4-diamine;

5-Bromo-N2-(1H-indol-4-yl)-N4-pyridin-2-ylmethyl-pyrimidine-2,4-diamine;

5-Bromo-N2-(1H-indazol-5-yl)-N4-pyridin-2-ylmethyl-pyrimidine-2,4-diamine;

N2-(1H-Indol-5-yl)-N4-pyridin-2-ylmethyl-pyrimidine-2,4-diamine;

N2-(1H-Indazol-6-yl)-N4-pyridin-2-ylmethyl-pyrimidine-2,4-diamine;

N2-(1H-Indol-5-yl)-N4-(2-pyridin-2-yl-ethyl)-pyrimidine-2,4-diamine;

N2-(1H-Indazol-5-yl)-N4-pyridin-2-ylmethyl-pyrimidine-2,4-diamine;

N2-(1H-Indazol-5-yl)-N4-(2-pyridin-2-yl-ethyl)-pyrimidine-2,4-diamine;

N2-(1H-Indazol-6-yl)-N4-(2-pyridin-2-yl-ethyl)-pyrimidine-2,4-diamine;

5-{5-Bromo-4-[(pyridin-2-ylmethyl)-amino]-pyrimidin-2-ylamino}-1,3-dihydro-benzoimidazol-2-one;

5-[5-Bromo-4-(2-pyridin-2-yl-ethylamino)-pyrimidin-2-ylamino]-1,3-dihydro-benzoimidazol-2-one;

5-{4-[(Pyridin-2-ylmethyl)-amino]-pyrimidin-2-ylamino}-1,3-dihydro-benzoimidazol-2-one;

5-[4-(2-Pyridin-2-yl-ethylamino)-pyrimidin-2-ylamino]-1,3-dihydro-benzoimidazol-2-one;

5-Bromo-N2-(1H-indazol-6-yl)-N4-pyridin-2-ylmethyl-pyrimidine-2,4-diamine;

5-{5-Bromo-4-[(pyridin-2-ylmethyl)-amino]-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-[5-Bromo-4-(2-pyridin-2-yl-ethylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-[4-(2-Pyridin-2-yl-ethylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;
5-Bromo-N2-(2-methyl-1H-indol-5-yl)-N4-(2-pyridin-2-yl-ethyl)-pyrimidine-2,4-diamine;
N2-(2-Methyl-1H-indol-5-yl)-N4-pyridin-2-ylmethyl-pyrimidine-2,4-diamine;
N2-(1H-Indol-6-yl)-N4-pyridin-2-ylmethyl-pyrimidine-2,4-diamine;
5-Bromo-N2-(2-methyl-1H-indol-5-yl)-N4-pyridin-2-ylmethyl-pyrimidine-2,4-diamine;
5-Bromo-N2-(1H-indol-6-yl)-N4-pyridin-2-ylmethyl-pyrimidine-2,4-diamine;
5-Bromo-N2-(1H-indol-6-yl)-N4-(2-pyridin-2-yl-ethyl)-pyrimidine2,4-diamine;
N2-(1H-Benzoimidazol-5-yl)-5-bromo-N4-pyridin-2-ylmethyl-pyrimidine-2,4-diamine;
N2-(1H-Benzoimidazol-5-yl)-5-bromo-N4-(2-pyridin-2-yl-ethyl)-pyrimidine-2,4-diamine;
3-[5-Bromo-4-(2-pyridin-2-yl-ethylamino)-pyrimidin-2-yl]-3H-benzoimidazol-5-ylamine
N2-(1H-Benzoimidazol-5-yl)-N4-pyridin-2-ylmethyl-pyrimidine-2,4-diamine;
5-Bromo-N2-(2-methyl-1H-benzoimidazol-5-yl)-N4-pyridin-2-ylmethyl-pyrimidine-2,4-diamine;
N2-(2-Methyl-1H-benzoimidazol-5-yl)-N4-pyridin-2-ylmethyl-pyrimidine-2,4-diamine;
5-Bromo-N2-(2-methyl-1H-benzoimidazol-5-yl)-N4-(2-pyridin-2-yl-ethyl)-pyrimidine-2,4-diamine;
5-Bromo-N2-(2,3-dihydro-1H-indol-5-yl)-N4-(2-pyridin-2-yl-ethyl)-pyrimidine-2,4-diamine;
N2-(2,3-Dihydro-1H-indol-5-yl)-N4-pyridin-2-ylmethyl-pyrimidine-2,4-diamine;
5-Bromo-N2-(1-methyl-1H-indol-5-yl)-N4-(2-pyridin-2-yl-ethyl)-pyrimidine-2,4-diamine;
N2-(1-Methyl-1H-indol-5-yl)-N4-pyridin-2-ylmethyl-pyrimidine-2,4-diamine;
5-Bromo-N2-(2,3-dihydro-1H-indol-5-yl)-N4-pyridin-2-ylmethyl-pyrimidine-2,4-diamine;
5-Bromo-N2-(1-methyl-1H-indol-5-yl)-N4-pyridin-2-ylmethyl-pyrimidine-2,4-diamine;
5-Fluoro-N4-pyridin-2-ylmethyl-N2-quinolin-6-yl-pyrimidine-2,4-diamine;
5-Bromo-N4-pyridin-2-ylmethyl-N2-quinolin-6-yl-pyrimidine-2,4-diamine;
5-Bromo-N2-(1H-indol-7-yl)-N4-(2-pyridin-2-yl-ethyl)-pyrimidine-2,4-diamine;
5-Bromo-N2-(1H-indol-7-yl)-N4-pyridin-2-ylmethyl-pyrimidine-2,4-diamine;
5-Bromo-N2-(1H-indazol-4-yl)-N4-pyridin-2-ylmethyl-pyrimidine-2,4-diamine;
6-[5-Bromo-4-[(pyridin-2-ylmethyl)-amino]-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;
5-Bromo-N2-(1H-indazol-4-yl)-N4-(2-pyridin-2-yl-ethyl)-pyrimidine-2,4-diamine;
5-Bromo-N4-(2-pyridin-2-yl-ethyl)-N2-quinolin-6-yl-pyrimidine-2,4-diamine;
5-Bromo-N4-pyridin-2-ylmethyl-N2-quinolin-5-yl-pyrimidine-2,4-diamine;
5-Bromo-N4-(2-pyridin-2-yl-ethyl)-N2-quinolin-5-yl-pyrimidine-2,4-diamine;
6-[5-Bromo-4-(2-pyridin-2-yl-ethylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;
5-Bromo-N4-pyridin-2-ylmethyl-N2-quinolin-8-yl-pyrimidine-2,4-diamine;
5-Bromo-N4-(2-pyridin-2-yl-ethyl)-N2-quinolin-8-yl-pyrimidine-2,4-diamine;

5-{5-Bromo-4-[(pyridin-2-ylmethyl)-amino]-pyrimidin-2-ylamino}-1H-indole-2-carboxylic acid; ethyl ester;

6-[5-Bromo-4-(2-trifluoromethyl-benzylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-Bromo-N2-(1H-indazol-5-yl)-N4-(2-trifluoromethyl-benzyl)-pyrimidine-2,4-diamine;

5-Bromo-N2-(1H-indazol-6-yl)-N4-(2-trifluoromethyl-benzyl)-pyrimidine-2,4-diamine;

5-Bromo-N2-(1-methyl-1H-indol-5-yl)-N4-(2-trifluoromethyl-benzyl)-pyrimidine-2,4-diamine;

5-Bromo-N2-(1H-indazol-7-yl)-N4-pyridin-2-ylmethyl-pyrimidine-2,4-diamine;

5-Bromo-N2-(1H-indazol-4-yl)-N4-(2-trifluoromethyl-benzyl)-pyrimidine-2,4-diamine;

6-{5-Bromo-4-[(pyridin-2-ylmethyl)-amino]-pyrimidin-2-ylamino}-3H-isobenzofuran-1-one;

N2-Benzothiazol-6-yl-5-bromo-N4-pyridin-2-ylmethyl-pyrimidine-2,4-diamine;

5-{5-Bromo-4-[(pyridin-2-ylmethyl)-amino]-pyrimidin-2-ylamino}-2-methyl-1H-indole-3-carbonitrile

5-Bromo-N4-pyridin-2-ylmethyl-N2-(1-pyridin-2-ylmethyl-1H-indazol-5-yl)-pyrimidine-2,4-diamine;

N2-(1-Benzyl-1H-indol-5-yl)-5-bromo-N4-pyridin-2-ylmethyl-pyrimidine-2,4-diamine;

5-Bromo-N4-pyridin-2-ylmethyl-N2-(1-pyridin-2-ylmethyl-1H-indol-5-yl)-pyrimidine-2,4-diamine;

N2-(1-Benzyl-1H-indazol-5-yl)-5-bromo-N4-pyridin-2-ylmethyl-pyrimidine-2,4-diamine;

5-Bromo-N2-(1-methyl-1H-indazol-5-yl)-N4-pyridin-2-ylmethyl-pyrimidine-2,4-diamine;

5-Bromo-N4-(4-methyl-cyclohexyl)-N2-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine;

5-Bromo-N4-(4-methyl-cyclohexyl)-N2-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine;

5-Bromo-N4-cyclohexylmethyl-N2-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine;

1-{5-Fluoro-4-[(pyridin-2-ylmethyl)-amino]-pyrimidin-2-yl}-3- (1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-ylamine

1-{5-Chloro-4-[(pyridin-2-ylmethyl)-amino]-pyrimidin-2-yl}-3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-ylamine

5-Fluoro-N2-(1H-indazol-5-yl)-N4-pyridin-2-ylmethyl-pyrimidine-2,4-diamine;

5-{5-Fluoro-4-[(pyridin-2-ylmethyl)-amino]-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-Chloro-N2-(1H-indazol-5-yl)-N4-pyridin-2-ylmethyl-pyrimidine-2,4-diamine;

5-{5-Chloro-4-[(pyridin-2-ylmethyl)-amino]-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-Fluoro-N4-(2-pyridin-2-yl-ethyl)-N2-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine;

5-Chloro-N4-(2-pyridin-2-yl-ethyl)-N2-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine;

5-Fluoro-N2-(1H-indazol-5-yl)-N4-(2-pyridin-2-yl-ethyl)-pyrimidine-2,4-diamine;

5-[5-Fluoro-4-(2-pyridin-2-yl-ethylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-Chloro-N2-(1H-indazol-5-yl)-N4-(2-pyridin-2-yl-ethyl)-pyrimidine-2,4-diamine;

5-[5-Chloro-4-(2-pyridin-2-yl-ethylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-{4-[(Pyridin-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-{5-Methoxy-4-[(pyridin-2-ylmethyl)-amino]-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-[5-Methoxy-4-(2-pyridin-2-yl-ethylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-[5-Methoxy-4-(2-trifluoromethyl-benzylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-{5-Bromo-4-[(cyclohex-1-enylmethyl)-amino]-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-[5-Bromo-4-(methyl-pyridin-2-ylmethyl-amino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-[5-Bromo-4-(4-methyl-cyclohexylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-[5-Bromo-4-(4-methyl-cyclohexylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-[5-Bromo-4-(cyclohexylmethyl-amino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-[5-Chloro-4-(2-trifluoromethyl-benzylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

2-(2-Oxo-2,3-dihydro-1H-indol-5-ylamino)-4-[(pyridin-2-ylmethyl)-amino]-pyrimidine-5-carbonitrile

5-{5-Methyl-4-[(pyridin-2-ylmethyl)-amino]-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

N2-(1H-Indazol-5-yl)-5-methyl-N4-pyridin-2-ylmethyl-pyrimidine-2,4-diamine;

5-Fluoro-N4-pyridin-2-ylmethyl-N2-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine;

5-Chloro-N4-pyridin-2-ylmethyl-N2-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine;

2-(2-Oxo-2,3-dihydro-1H-indol-5-ylamino)-4-(2-trifluoromethyl-benzylamino)-pyrimidine-5-carbonitrile

5-[4-[Methyl-(2-pyridin-2-yl-ethyl)-amino]-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-Bromo-N4-cyclohex-1-enylmethyl-N2-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine;

N2-(1H-Indazol-5-yl)-N4-pyridin-2-ylmethyl-5-trifluoromethyl-pyrimidine-2,4-diamine;

5-[5-Trifluoromethyl-4-(2-trifluoromethyl-benzylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

6-{2-[(Pyridin-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-4-ylamino}-1,3-dihydro-indol-2-one;

5-[5-Bromo-4-(piperidin-4-ylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-[4-(1-Acetyl-piperidin-4-ylamino)-5-bromo-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

2-(2-Oxo-2,3-dihydro-1H-indol-6-ylamino)-4-[(pyridin-2-ylmethyl)-amino]-pyrimidine-5-carbonitrile

5-{4-[(3-Methyl-pyridin-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

6-{4-[(3-Methyl-pyridin-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

4-[5-Bromo-2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-pyrimidin-4-ylamino]-piperidine-1-carboxylic acid; tert-butyl ester;

5-[5-Bromo-4-(1-methanesulfonyl-piperidin-4-ylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-[5-Bromo-4-(piperidin-3-ylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

4-[5-Bromo-2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-pyrimidin-4-ylamino]-piperidine-1-carboxylic acid; ethylamide

3-[5-Bromo-2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-pyrimidin-4-ylamino]-piperidine-1-carboxylic acid; ethylamide

5-[4-(1-Benzoyl-piperidin-4-ylamino)-5-bromo-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

6-[4-(3-Methanesulfonyl-benzylamino)-5-methoxy-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

6-[4-(3-Methanesulfonyl-benzylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

6-[4-(3-Methanesulfonyl-benzylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-[4-(1-Benzenesulfonyl-piperidin-4-ylamino)-5-bromo-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-[4-(3-Methanesulfonyl-benzylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

6-{5-Chloro-4-[(piperidin-3-ylmethyl)-amino]-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

6-{5-Chloro-4-[(1-methanesulfonyl-piperidin-3-ylmethyl)-amino]-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

6-{5-Bromo-4-[(piperidin-3-ylmethyl)-amino]-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

6-{5-Bromo-4-[(1-methanesulfonyl-piperidin-3-ylmethyl)-amino]-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-[5-Fluoro-4-(3-methanesulfonyl-benzylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-{5-Bromo-4-[(1-hydroxy-cyclohexylmethyl)-amino]-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

and pharmaceutically acceptable salt, prodrug, hydrate or solvate of the aforementioned compounds.

This invention also relates to a method for the treatment of abnormal cell growth in a mammal, including a human, comprising administering to said mammal an amount of a compound of the formula 1, as defined above, or a pharmaceutically acceptable salt, solvate or prodrug thereof, that is effective in treating abnormal cell growth. In one embodiment of this method, the abnormal cell growth is cancer, including, but not limited to, lung cancer, bone cancer, pancreatic cancer, skin cancer, cancer of the head or neck, cutaneous or intraocular melanoma, uterine cancer, ovarian cancer, rectal cancer, cancer of the anal region, stomach cancer, colon cancer, breast cancer, uterine cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, Hodgkin's Disease, cancer of the esophagus, cancer of the small intestine, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the adrenal gland, sarcoma of soft tissue, cancer of the urethra, cancer of the penis, prostate cancer, chronic or acute leukemia, lymphocytic lymphomas, cancer of the bladder, cancer of the kidney or ureter, renal cell carcinoma, carcinoma of the renal pelvis, neoplasms of the central nervous system (CNS), primary CNS lymphoma, spinal axis tumors, brain stem glioma, pituitary adenoma, or a combination of one or more of the foregoing cancers. In one embodiment the method comprises comprising administering to a mammal an amount of a compound of formula 1 that is effective in treating said cancer solid tumor. In one preferred embodiment the solid tumor is breast, lung, colon, brain, prostate, stomach, pancreatic, ovarian, skin (melanoma), endocrine, uterine, testicular, and bladder cancer.

In another embodiment of said method, said abnormal cell growth is a benign proliferative disease, including, but not limited to, psoriasis, benign prostatic hypertrophy or restinosis.

This invention also relates to a method for the treatment of abnormal cell growth in a mammal which comprises administering to said mammal an amount of a compound of formula 1, or a pharmaceutically acceptable salt, solvate or prodrug thereof, that is effective in treating abnormal cell growth in combination with an anti-tumor agent selected from the group consisting of mitotic inhibitors, alkylating agents, anti-metabolites, intercalating antibiotics, growth factor inhibitors, cell cycle inhibitors, enzymes, topoisomerase inhibitors, biological response modifiers, antibodies, cytotoxics, anti-hormones, and anti-androgens.

This invention also relates to a pharmaceutical composition for the treatment of abnormal cell growth in a mammal, including a human, comprising an amount of a compound of the formula 1, as defined above, or a pharmaceutically acceptable salt, solvate or prodrug thereof, that is effective in treating abnormal cell growth, and a pharmaceutically acceptable carrier. In one embodiment of said composition, said abnormal cell growth is cancer, including, but not limited to, lung cancer, bone cancer, pancreatic cancer, skin cancer, cancer of the head or neck, cutaneous or intraocular melanoma, uterine cancer, ovarian cancer, rectal cancer, cancer of the anal region, stomach cancer, colon cancer, breast cancer, uterine cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, Hodgkin's Disease, cancer of the esophagus, cancer of the small intestine, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the adrenal gland, sarcoma of soft tissue, cancer of the urethra, cancer of the penis, prostate cancer, chronic or acute leukemia, lymphocytic lymphomas, cancer of the bladder, cancer of the kidney or ureter, renal cell carcinoma, carcinoma of the renal pelvis, neoplasms of the central nervous system (CNS), primary CNS lymphoma, spinal axis tumors, brain stem glioma, pituitary adenoma, or a combination of one or more of the foregoing cancers. In another embodiment of said pharmaceutical composition, said abnormal cell growth is a benign proliferative disease, including, but not limited to, psoriasis, benign prostatic hypertrophy or restinosis.

The invention also relates to a pharmaceutical composition for the treatment of abnormal cell growth in a mammal, including a human, which comprises an amount of a compound of formula 1, as defined above, or a pharmaceutically acceptable salt, solvate or prodrug thereof, that is effective in treating abnormal cell growth in combination with a pharmaceutically acceptable carrier and an anti-tumor agent selected from the group consisting of mitotic inhibitors, alkylating agents, anti-metabolites, intercalating antibiotics, growth factor inhibitors, cell cycle inhibitors, enzymes, topoisomerase inhibitors, biological response modifiers, anti-hormones, and anti-androgens.

This invention also relates to a method for the treatment of a disorder associated with angiogenesis in a mammal, including a human, comprising administering to said mammal an amount of a compound of the formula 1, as defined above, or a pharmaceutically acceptable

salt, solvate or prodrug thereof, that is effective in treating said disorder. Such disorders include cancerous tumors such as melanoma; ocular disorders such as age-related macular degeneration, presumed ocular histoplasmosis syndrome, and retinal neovascularization from proliferative diabetic retinopathy; rheumatoid arthritis; bone loss disorders such as osteoporosis, Paget's disease, humoral hypercalcemia of malignancy, hypercalcemia from tumors metastatic to bone, and osteoporosis induced by glucocorticoid treatment; coronary restenosis; and certain microbial infections including those associated with microbial pathogens selected from adenovirus, hantaviruses, *Borrelia burgdorferi, Yersinia spp., Bordetella pertussis*, and group A *Streptococcus*.

This invention also relates to a method of (and to a pharmaceutical composition for) treating abnormal cell growth in a mammal which comprise an amount of a compound of formula 1, or a pharmaceutically acceptable salt, solvate or prodrug thereof, and an amount of one or more substances selected from anti-angiogenesis agents, signal transduction inhibitors, and antiproliferative agents, which amounts are together effective in treating said abnormal cell growth.

Anti-angiogenesis agents, such as MMP-2 (matrix-metalloprotienase 2) inhibitors, MMP-9 (matrix-metalloprotienase 9) inhibitors, and COX-II (cyclooxygenase II) inhibitors, can be used in conjunction with a compound of formula 1 in the methods and pharmaceutical compositions described herein. Examples of useful COX-II inhibitors include CELEBREX™ (alecoxib), valdecoxib, and rofecoxib. Examples of useful matrix metalloproteinase inhibitors are described in WO 96/33172 (published October 24, 1996), WO 96/27583 (published March 7, 1996), European Patent Application No. 97304971.1 (filed July 8, 1997), European Patent Application No. 99308617.2 (filed October 29, 1999), WO 98/07697 (published February 26, 1998), WO 98/03516 (published January 29, 1998), WO 98/34918 (published August 13, 1998), WO 98/34915 (published August 13, 1998), WO 98/33768 (published August 6, 1998), WO 98/30566 (published July 16, 1998), European Patent Publication 606,046 (published July 13, 1994), European Patent Publication 931,788 (published July 28, 1999), WO 90/05719 (published May 331, 1990), WO 99/52910 (published October 21, 1999), WO 99/52889 (published October 21, 1999), WO 99/29667 (published June 17, 1999), PCT International Application No. PCT/IB98/01113 (filed July 21, 1998), European Patent Application No. 99302232.1 (filed March 25, 1999), Great Britain patent application number 9912961.1 (filed June 3, 1999), United States Provisional Application No. 60/148,464 (filed August 12, 1999), United States Patent 5,863,949 (issued January 26, 1999), United States Patent 5,861,510 (issued January 19, 1999), and European Patent Publication 780,386 (published June 25, 1997), all of which are herein incorporated by reference in their entirety. Preferred MMP-2 and MMP-9 inhibitors are those that have little or no activity inhibiting MMP-1. More preferred, are those that selectively inhibit MMP-

2 and/or MMP-9 relative to the other matrix-metalloproteinases (*i.e.* MMP-1, MMP-3, MMP-4, MMP-5, MMP-6, MMP-7, MMP-8, MMP-10, MMP-11, MMP-12, and MMP-13).

Some specific examples of MMP inhibitors useful in combination with the compounds of the present invention are AG-3340, RO 32-3555, RS 13-0830, and the compounds recited in the following list:

3-[[4-(4-fluoro-phenoxy)-benzenesulfonyl]-(1-hydroxycarbamoyl-cyclopentyl)-amino]-propionic acid;

3-exo-3-[4-(4-fluoro-phenoxy)-benzenesulfonylamino]-8-oxa-bicyclo[3.2.1]octane-3-carboxylic acid hydroxyamide;

(2R, 3R) 1-[4-(2-chloro-4-fluoro-benzyloxy)-benzenesulfonyl]-3-hydroxy-3-methyl-piperidine-2-carboxylic acid hydroxyamide;

4-[4-(4-fluoro-phenoxy)-benzenesulfonylamino]-tetrahydro-pyran-4-carboxylic acid hydroxyamide;

3-[[4-(4-fluoro-phenoxy)-benzenesulfonyl]-(1-hydroxycarbamoyl-cyclobutyl)-amino]-propionic acid;

4-[4-(4-chloro-phenoxy)-benzenesulfonylamino]-tetrahydro-pyran-4-carboxylic acid hydroxyamide;

3-[4-(4-chloro-phenoxy)-benzenesulfonylamino]-tetrahydro-pyran-3-carboxylic acid hydroxyamide;

(2R, 3R) 1-[4-(4-fluoro-2-methyl-benzyloxy)-benzenesulfonyl]-3-hydroxy-3-methyl-piperidine-2-carboxylic acid hydroxyamide;

3-[[4-(4-fluoro-phenoxy)-benzenesulfonyl]-(1-hydroxycarbamoyl-1-methyl-ethyl)-amino]-propionic acid;

3-[[4-(4-fluoro-phenoxy)-benzenesulfonyl]-(4-hydroxycarbamoyl-tetrahydro-pyran-4-yl)-amino]-propionic acid;

3-exo-3-[4-(4-chloro-phenoxy)-benzenesulfonylamino]-8-oxa-bicyclo[3.2.1]octane-3-carboxylic acid hydroxyamide;

3-endo-3-[4-(4-fluoro-phenoxy)-benzenesulfonylamino]-8-oxa-bicyclo[3.2.1]octane-3-carboxylic acid hydroxyamide; and

3-[4-(4-fluoro-phenoxy)-benzenesulfonylamino]-tetrahydro-furan-3-carboxylic acid hydroxyamide;

and pharmaceutically acceptable salts, solvates and prodrugs of said compounds.

The compounds of formula 1, and the pharmaceutically acceptable salts, solvates and prodrugs thereof, can also be used in combination with signal transduction inhibitors, such as agents that can inhibit EGFR (epidermal growth factor receptor) responses, such as EGFR antibodies, EGF antibodies, and molecules that are EGFR inhibitors; VEGF (vascular endothelial growth factor) inhibitors; and erbB2 receptor inhibitors, such as organic molecules

or antibodies that bind to the erbB2 receptor, for example, HERCEPTIN™ (Genentech, Inc. of South San Francisco, California, USA).

EGFR inhibitors are described in, for example in WO 95/19970 (published July 27, 1995), WO 98/14451 (published April 9, 1998), WO 98/02434 (published January 22, 1998), and United States Patent 5,747,498 (issued May 5, 1998). EGFR-inhibiting agents include, but are not limited to, CI-1033 (Pfizer Inc.), the monoclonal antibodies C225 and anti-EGFR 22Mab (ImClone Systems Incorporated of New York, New York, USA), the compounds ZD-1839 (AstraZeneca), BIBX-1382 (Boehringer Ingelheim), MDX-447 (Medarex Inc. of Annandale, New Jersey, USA), and OLX-103 (Merck & Co. of Whitehouse Station, New Jersey, USA), VRCTC-310 (Ventech Research) and EGF fusion toxin (Seragen Inc. of Hopkinton, Massachusettes).

VEGF inhibitors, for example CP-547,632 and AG-13736 (Pfizer, Inc.), SU-5416 and SU-6668 (Sugen Inc. of South San Francisco, California, USA), can also be combined with a compound of formula 1. VEGF inhibitors are described in, for example in WO 99/24440 (published May 20, 1999), PCT International Application PCT/IB99/00797 (filed May 3, 1999), in WO 95/21613 (published August 17, 1995), WO 99/61422 (published December 2, 1999), United States Patent 5,834,504 (issued November 10, 1998), WO 98/50356 (published November 12, 1998), United States Patent 5,883,113 (issued March 16, 1999), United States Patent 5,886,020 (issued March 23, 1999), United States Patent 5,792,783 (issued August 11, 1998), WO 99/10349 (published March 4, 1999), WO 97/32856 (published September 12, 1997), WO 97/22596 (published June 26, 1997), WO 98/54093 (published December 3, 1998), WO 98/02438 (published January 22, 1998), WO 99/16755 (published April 8, 1999), and WO 98/02437 (published January 22, 1998), all of which are herein incorporated by reference in their entirety. Other examples of some specific VEGF inhibitors are IM862 (Cytran Inc. of Kirkland, Washington, USA); anti-VEGF monoclonal antibody of Genentech, Inc. of South San Francisco, California; and angiozyme, a synthetic ribozyme from Ribozyme (Boulder, Colorado) and Chiron (Emeryville, California).

ErbB2 receptor inhibitors, such as CP-724,714 (Pfizer, Inc.), GW-282974 (Glaxo Wellcome plc), and the monoclonal antibodies AR-209 (Aronex Pharmaceuticals Inc. of The Woodlands, Texas, USA) and 2B-1 (Chiron), may be administered in combination with a compound of formula 1. Such erbB2 inhibitors include those described in WO 98/02434 (published January 22, 1998), WO 99/35146 (published July 15, 1999), WO 99/35132 (published July 15, 1999), WO 98/02437 (published January 22, 1998), WO 97/13760 (published April 17, 1997), WO 95/19970 (published July 27, 1995), United States Patent 5,587,458 (issued December 24, 1996), and United States Patent 5,877,305 (issued March 2, 1999), each of which is herein incorporated by reference in its entirety. ErbB2 receptor inhibitors useful in the present invention are also described in United States Provisional

Application No. 60/117,341, filed January 27, 1999, and in United States Provisional Application No. 60/117,346, filed January 27, 1999, both of which are herein incorporated by reference in their entirety.

Other antiproliferative agents that may be used with the compounds of the present invention include inhibitors of HDI (CI-994, Pfizer Inc.), MEK (CI-1040, Pfizer Inc.), the enzyme farnesyl protein transferase and the receptor tyrosine kinase PDGFr, including the compounds disclosed and claimed in the following United States patent applications: 09/221946 (filed December 28, 1998); 09/454058 (filed December 2, 1999); 09/501163 (filed February 9, 2000); 09/539930 (filed March 31, 2000); 09/202796 (filed May 22, 1997); 09/384339 (filed August 26, 1999); and 09/383755 (filed August 26, 1999); and the compounds disclosed and claimed in the following United States provisional patent applications: 60/168207 (filed November 30, 1999); 60/170119 (filed December 10, 1999); 60/177718 (filed January 21, 2000); 60/168217 (filed November 30, 1999), and 60/200834 (filed May 1, 2000). Each of the foregoing patent applications and provisional patent applications is herein incorporated by reference in their entirety.

A compound of formula 1 may also be used with other agents useful in treating abnormal cell growth or cancer, including, but not limited to, agents capable of enhancing antitumor immune responses, such as CTLA4 (cytotoxic lymphocite antigen 4) antibodies, and other agents capable of blocking CTLA4; and anti-proliferative agents such as other farnesyl protein transferase inhibitors, for example the farnesyl protein transferase inhibitors described in the references cited in the "Background" section, *supra*. Specific CTLA4 antibodies that can be used in the present invention include those described in United States Provisional Application 60/113,647 (filed December 23, 1998) which is herein incorporated by reference in its entirety.

"Abnormal cell growth", as used herein, unless otherwise indicated, refers to cell growth that is independent of normal regulatory mechanisms (e.g., loss of contact inhibition). This includes the abnormal growth of: (1) tumor cells (tumors) that proliferate by expressing a mutated tyrosine kinase or overexpression of a receptor tyrosine kinase; (2) benign and malignant cells of other proliferative diseases in which aberrant tyrosine kinase activation occurs; (4) any tumors that proliferate by receptor tyrosine kinases; (5) any tumors that proliferate by aberrant serine/threonine kinase activation; and (6) benign and malignant cells of other proliferative diseases in which aberrant serine/threonine kinase activation occurs..

The term "treating", as used herein, unless otherwise indicated, means reversing, alleviating, inhibiting the progress of, or preventing the disorder or condition to which such term applies, or one or more symptoms of such disorder or condition. The term "treatment", as used herein, unless otherwise indicated, refers to the act of treating as "treating" is defined immediately above.

The term "halo", as used herein, unless otherwise indicated, includes fluoro, chloro, bromo or iodo. Preferred halo groups are fluoro and chloro.

The term "alkyl", as used herein, unless otherwise indicated, includes saturated monovalent hydrocarbon radicals having straight, cyclic (including mono- or multi-cyclic moieties) or branched moieties. It is understood that for said alkyl group to include cyclic moieties it must contain at least three carbon atoms.

The term "cycloalkyl", as used herein, unless otherwise indicated, includes saturated monovalent hydrocarbon radicals having cyclic (including mono- or multi-cyclic) moieties.

The term "alkenyl", as used herein, unless otherwise indicated, includes alkyl groups, as defined above, having at least one carbon-carbon double bond.

The term "alkynyl", as used herein, unless otherwise indicated, includes alkyl groups, as defined above, having at least one carbon-carbon triple bond.

The term "aryl", as used herein, unless otherwise indicated, includes an organic radical derived from an aromatic hydrocarbon by removal of one hydrogen, such as phenyl or naphthyl.

The term "alkoxy", as used herein, unless otherwise indicated, includes –O-alkyl groups wherein alkyl is as defined above.

The term "4 to 10 membered heterocyclic", as used herein, unless otherwise indicated, includes aromatic and non-aromatic heterocyclic groups containing one or more heteroatoms each selected from O, S and N, wherein each heterocyclic group has from 4 to 10 atoms in its ring system. Non-aromatic heterocyclic groups include groups having only 4 atoms in their ring system, but aromatic heterocyclic groups must have at least 5 atoms in their ring system. The heterocyclic groups include benzo-fused ring systems and ring systems substituted with one or more oxo moieties. An example of a 4 membered heterocyclic group is azetidinyl (derived from azetidine). An example of a 5 membered heterocyclic group is thiazolyl and an example of a 10 membered heterocyclic group is quinolinyl. Examples of non-aromatic heterocyclic groups are pyrrolidinyl, tetrahydrofuranyl, tetrahydrothienyl, tetrahydropyranyl, tetrahydrothiopyranyl, piperidino, morpholino, thiomorpholino, thioxanyl, piperazinyl, azetidinyl, oxetanyl, thietanyl, homopiperidinyl, oxepanyl, thiepanyl, oxazepinyl, diazepinyl, thiazepinyl, 1,2,3,6-tetrahydropyridinyl, 2-pyrrolinyl, 3-pyrrolinyl, indolinyl, 2H-pyranyl, 4H-pyranyl, dioxanyl, 1,3-dioxolanyl, pyrazolinyl, dithianyl, dithiolanyl, dihydropyranyl, dihydrothienyl, dihydrofuranyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, 3-azabicyclo[3.1.0]hexanyl, 3-azabicyclo[4.1.0]heptanyl, 3H-indolyl and quinolizinyl. Examples of aromatic heterocyclic groups are pyridinyl, imidazolyl, pyrimidinyl, pyrazolyl, triazolyl, pyrazinyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, oxazolyl, isothiazolyl, pyrrolyl, quinolinyl, isoquinolinyl, indolyl, benzimidazolyl, benzofuranyl, cinnolinyl, indazolyl, indolizinyl, phthalazinyl, pyridazinyl, triazinyl, isoindolyl, pteridinyl, purinyl, oxadiazolyl, thiadiazolyl, furazanyl, benzofurazanyl, benzothiophenyl, benzothiazolyl, benzoxazolyl, quinazolinyl, quinoxalinyl, naphthyridinyl, and

furopyridinyl. The foregoing groups, as derived from the compounds listed above, may be C-attached or N-attached where such is possible. For instance, a group derived from pyrrole may be pyrrol-1-yl (N-attached) or pyrrol-3-yl (C-attached).

The term "Me" means methyl, "Et" means ethyl, and "Ac" means acetyl.

In the definition of $X^1$ above, the $-(CR^1R^2)_m-$ and $(CR^{16}R^{17})_k$ moieties, and other similar moieties, as indicated above, may vary in their definition of $R^1$, $R^2$, $R^{16}$ and $R^{17}$ for each iteration of the subscript (ie, m, k, etc) above 1. Thus, $-(CR^1R^2)_m-$ may include $-CH_2C(Me)(Et)-$ where m is 2.

The phrase "pharmaceutically acceptable salt(s)", as used herein, unless otherwise indicated, includes salts of acidic or basic groups which may be present in the compounds of the present invention. The compounds of the present invention that are basic in nature are capable of forming a wide variety of salts with various inorganic and organic acids. The acids that may be used to prepare pharmaceutically acceptable acid addition salts of such basic compounds of are those that form non-toxic acid addition salts, i.e., salts containing pharmacologically acceptable anions, such as the hydrochloride, hydrobromide, hydroiodide, nitrate, sulfate, bisulfate, phosphate, acid phosphate, isonicotinate, acetate, lactate, salicylate, citrate, acid citrate, tartrate, pantothenate, bitartrate, ascorbate, succinate, maleate, gentisinate, fumarate, gluconate, glucuronate, saccharate, formate, benzoate, glutamate, methanesulfonate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate and pamoate [i.e., 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)] salts. The compounds of the present invention that include a basic moiety, such as an amino group, may form pharmaceutically acceptable salts with various amino acids, in addition to the acids mentioned above.

Those compounds of the present invention that are acidic in nature are capable of forming base salts with various pharmacologically acceptable cations. Examples of such salts include the alkali metal or alkaline earth metal salts and, particularly, the calcium, magnesium, sodium and potassium salts of the compounds of the present invention.

Certain functional groups contained within the compounds of the present invention can be substituted for bioisosteric groups, that is, groups which have similar spatial or electronic requirements to the parent group, but exhibit differing or improved physicochemical or other properties. Suitable examples are well known to those of skill in the art, and include, but are not limited to moieties described in Patini et al., Chem. Rev, 1996, 96, 3147-3176 and references cited therein.

The compounds of the present invention have asymmetric centers and therefore exist in different enantiomeric and diastereomeric forms. This invention relates to the use of all optical isomers and stereoisomers of the compounds of the present invention, and mixtures thereof, and to all pharmaceutical compositions and methods of treatment that may employ or contain them. The compounds of formula 1 may also exist as tautomers. This invention relates to the use of all such tautomers and mixtures thereof.

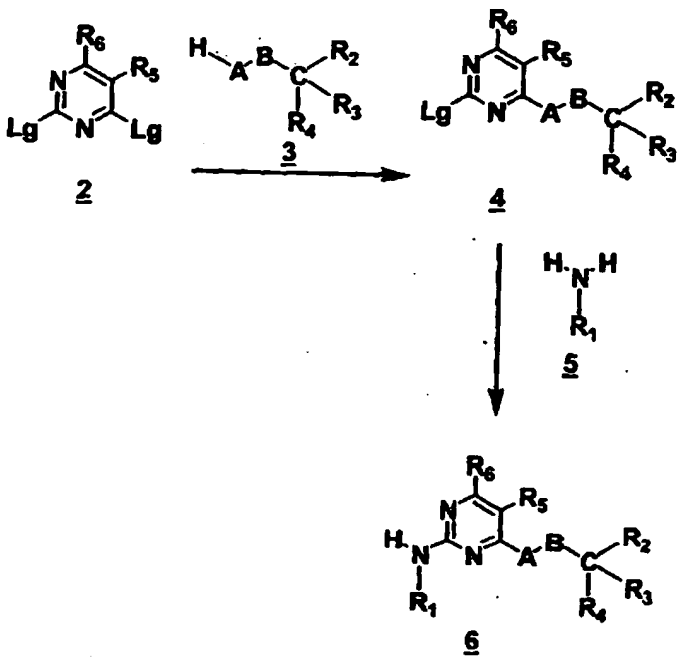
The subject invention also includes isotopically-labelled compounds, and the pharmaceutically acceptable salts, solvates and prodrugs thereof, which are identical to those recited in formula 1, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine and chlorine, such as $^{2}H$, $^{3}H$, $^{13}C$, $^{14}C$, $^{15}N$, $^{18}O$, $^{17}O$, $^{35}S$, $^{18}F$, and $^{36}Cl$, respectively. Compounds of the present invention, prodrugs thereof, and pharmaceutically acceptable salts of said compounds or of said prodrugs which contain the aforementioned isotopes and/or other isotopes of other atoms are within the scope of this invention. Certain isotopically-labelled compounds of the present invention, for example those into which radioactive isotopes such as $^{3}H$ and $^{14}C$ are incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, i.e., $^{3}H$, and carbon-14, i.e., $^{14}C$, isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium, i.e., $^{2}H$, can afford certain therapeutic advantages resulting from greater metabolic stability, for example increased *in vivo* half-life or reduced dosage requirements and, hence, may be preferred in some circumstances. Isotopically labelled compounds of formula 1 of this invention and prodrugs thereof can generally be prepared by carrying out the procedures disclosed in the Schemes and/or in the Examples and Preparations below, by substituting a readily available isotopically labelled reagent for a non-isotopically labelled reagent.

This invention also encompasses pharmaceutical compositions containing and methods of treating bacterial infections through administering prodrugs of compounds of the formula 1. Compounds of formula 1 having free amino, amido, hydroxy or carboxylic groups can be converted into prodrugs. Prodrugs include compounds wherein an amino acid residue, or a polypeptide chain of two or more (e.g., two, three or four) amino acid residues is covalently joined through an amide or ester bond to a free amino, hydroxy or carboxylic acid group of compounds of formula 1. The amino acid residues include but are not limited to the 20 naturally occurring amino acids commonly designated by three letter symbols and also includes 4-hydroxyproline, hydroxylysine, demosine, isodemosine, 3-methylhistidine, norvalin, beta-alanine, gamma-aminobutyric acid, citrulline homocysteine, homoserine, ornithine and methionine sulfone. Additional types of prodrugs are also encompassed. For instance, free carboxyl groups can be derivatized as amides or alkyl esters. Free hydroxy groups may be derivatized using groups including but not limited to hemisuccinates, phosphate esters, dimethylaminoacetates, and phosphoryloxymethyloxycarbonyls, as outlined in *Advanced Drug Delivery Reviews*, 1996, *19*, 115. Carbamate prodrugs of hydroxy and amino groups are also included, as are carbonate prodrugs, sulfonate esters and sulfate esters of hydroxy groups. Derivatization of hydroxy groups as (acyloxy)methyl and (acyloxy)ethyl ethers wherein the acyl group may be an alkyl

ester, optionally substituted with groups including but not limited to ether, amine and carboxylic acid functionalities, or where the acyl group is an amino acid ester as described above, are also encompassed. Prodrugs of this type are described in *J. Med. Chem.* 1996, 39, 10. Free amines can also be derivatized as amides, sulfonamides or phosphonamides. All of these prodrug moieties may incorporate groups including but not limited to ether, amine and carboxylic acid functionalities.

## Detailed Description Of The Invention

The compounds of formula 1 can be prepared using the following synthetic scheme 1. The substituents in scheme 1 have the same meaning as the substituents defined for formula 1. The substituent Lg in the compounds of formulas 2 and 4 is a leaving group. Leaving groups are well-known to those of ordinary skill in the art. Applicants also direct the reader's attention to the Experimental section for particular examples of leaving group employed in the preparation of the compounds of the present invention.



Scheme 1

Necessary starting materials may be purchased and used directly or alternatively, starting materials can be prepared by one skilled in the art utilizing known procedures obtained from standard chemistry references (such as, Organic Synthesis (McGraw Hill) Michael Smith). It is understood that starting materials may be optionally protected as to not interfere with a desired chemical reaction (see Protecting Groups in Organic Synthesis (Wiley-Interscience), Green and Wutts). Subsequent de-protection of potentially interfering functional group may be effected at a later appropriate time to obtain the necessary desired material. A pyrimidine of the

general formula I may be purchased or prepared from known materials by one skilled in the art. Lg is defined as a displaceable leaving group that includes halogens and sulfonyl groups.

Using methods known in the literature by one skilled in the art, a pyrimidine of formula 2 may be reacted together with a compound of formula 3, optionally in the presence of a suitable base and optionally in the presence of a suitable inert solvent and at a temperature range of 0oC to 150°C. Suitable bases employed may be the following but not limited to (i) organic bases, for example triethylamine, or diisopropylethylamine and (ii) inorganic bases such as potassium carbonate or cesium carbonate. The reaction may be performed neat or carried out in a suitable inert solvent. Examples of suitable inert solvents are but not limited to tetrahydrofuran, 1,4-dioxane, dimethylformamide, n-methyl pyrrolidin-2-one, ethanol, butanol, dichloromethane, or acetonitrile. Followed by the next reaction in which pyrimidine of formula 4 may be reacted together with amine compounds of formula IV optionally in the presence of a suitable base and optionally in the presence of a suitable inert solvent and at a temperature range of 0°C to 150°C conveniently at or near reflux to obtain compounds of formula 6. The reaction may be performed neat or optionally carried out in a suitable inert solvent. Examples of suitable inert solvents are but not limited to tetrahydrofuran, 1,4-dioxane, dimethylformamide, n-methyl pyrrolidin-2-one, ethanol, butanol, dichloromethane, dimethyl sulfoxide or acetonitrile.

Compounds of formula 6, if optional protecting groups are present would be removed using standard techniques well-known to those of ordinary skill in the art, see for example, Protecting Groups in Organic Synthesis (Wiley-Interscience), Green and Wutts. These methods are known to those skilled in the art and include a) removal of a protecting group by methods outlined in T. W. Greene and P.G.M. Wuts, "Protective Groups in Organic Synthesis", Second Edition, John Wiley and Sons, New York, 1991; b) displacement of a leaving group (halide, mesylate, tosylate, etc) with a primary or secondary amine, thiol or alcohol to form a secondary or tertiary amine, thioether or ether, respectively; c) treatment of phenyl (or substituted phenyl) carbamates with primary of secondary amines to form the corresponding ureas as in Thavonekham, B et. al. Synthesis (1997), 10, p1189; d) reduction of propargyl or homopropargyl alcohols or N-BOC protected primary amines to the corresponding E-allylic or E-homoallylic derivatives by treatment with sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al) as in Denmark, S. E.; Jones, T. K. J. Org. Chem. (1982) 47, 4595-4597 or van Benthem, R. A. T. M.; Michels, J. J.; Speckamp, W. N. Synlett (1994), 368-370; e) reduction of alkynes to the corresponding Z-alkene derivatives by treatment hydrogen gas and a Pd catalyst as in Tomassy, B. et. al. Synth. Commun. (1998), 28, p1201 f) treatment of primary and secondary amines with an isocyanate, acid chloride (or other activated carboxylic acid derivative), alkyl/aryl chloroformate or sulfonyl chloride to provide the corresponding urea, amide, carbamate or sulfonamide; g) reductive amination of a primary or secondary amine using $R^1CH(O)$; and h) treatment of alcohols with an isocyanate, acid chloride (or other activated carboxylic acid

derivative), alkyl/aryl chloroformate or sulfonyl chloride to provide the corresponding carbamate, ester, carbonate or sulfonic acid ester.

The compounds of the present invention may have asymmetric carbon atoms. Diasteromeric mixtures can be separated into their individual diastereomers on the basis of their physical chemical differences by methods known to those skilled in the art, for example, by chromatography or fractional crystallization. Enantiomers can be separated by converting the enantiomeric mixtures into a diastereomric mixture by reaction with an appropriate optically active compound (e.g., alcohol), separating the diastereomers and converting (e.g., hydrolyzing) the individual diastereomers to the corresponding pure enantiomers. All such isomers, including diastereomeric mixtures and pure enantiomers are considered as part of the invention.

The compounds of formulas 1 that are basic in nature are capable of forming a wide variety of different salts with various inorganic and organic acids. Although such salts must be pharmaceutically acceptable for administration to animals, it is often desirable in practice to initially isolate the compound of formula 1 from the reaction mixture as a pharmaceutically unacceptable salt and then simply convert the latter back to the free base compound by treatment with an alkaline reagent and subsequently convert the latter free base to a pharmaceutically acceptable acid addition salt. The acid addition salts of the base compounds of this invention are readily prepared by treating the base compound with a substantially equivalent amount of the chosen mineral or organic acid in an aqueous solvent medium or in a suitable organic solvent, such as methanol or ethanol. Upon careful evaporation of the solvent, the desired solid salt is readily obtained. The desired acid salt can also be precipitated from a solution of the free base in an organic solvent by adding to the solution an appropriate mineral or organic acid.

Those compounds of formula 1 that are acidic in nature are capable of forming base salts with various pharmacologically acceptable cations. Examples of such salts include the alkali metal or alkaline-earth metal salts and particularly, the sodium and potassium salts. These salts are all prepared by conventional techniques. The chemical bases which are used as reagents to prepare the pharmaceutically acceptable base salts of this invention are those which form non-toxic base salts with the acidic compounds of formula 1. Such non-toxic base salts include those derived from such pharmacologically acceptable cations as sodium, potassium calcium and magnesium, etc. These salts can easily be prepared by treating the corresponding acidic compounds with an aqueous solution containing the desired pharmacologically acceptable cations, and then evaporating the resulting solution to dryness, preferably under reduced pressure. Alternatively, they may also be prepared by mixing lower alkanolic solutions of the acidic compounds and the desired alkali metal alkoxide together, and then evaporating the resulting solution to dryness in the same manner as before. In either case, stoichiometric quantities of reagents are preferably employed in order to ensure completeness of reaction and

maximum yields of the desired final product. Since a single compound of the present invention may include more than one acidic or basic moieties, the compounds of the present invention may include mono, di or tri-salts in a single compound.

The compounds of the present invention are potent inhibitors of the FAK protein tyrosine kinases, and thus are all adapted to therapeutic use as antiproliferative agents (e.g., anticancer), antitumor (e.g., effective against solid tumors), antiangiogenesis (e.g., stop or prevent proliferationation of blood vessels) in mammals, particularly in humans. In particular, the compounds of the present invention are useful in the prevention and treatment of a variety of human hyperproliferative disorders such as malignant and benign tumors of the liver, kidney, bladder, breast, gastric, ovarian, colorectal, prostate, pancreatic, lung, vulval, thyroid, hepatic carcinomas, sarcomas, glioblastomas, head and neck, and other hyperplastic conditions such as benign hyperplasia of the skin (e.g., psoriasis) and benign hyperplasia of the prostate (e.g., BPH). It is, in addition, expected that a compound of the present invention may possess activity against a range of leukemias and lymphoid malignancies.

In one preferred embodiment of the present invention cancer is selected from lung cancer, bone cancer, pancreatic cancer, gastric, skin cancer, cancer of the head or neck, cutaneous or intraocular melanoma, uterine cancer, ovarian cancer, gynecological, rectal cancer, cancer of the anal region, stomach cancer, colon cancer, breast cancer, uterine cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, Hodgkin's Disease, cancer of the esophagus, cancer of the small intestine, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the adrenal gland, sarcoma of soft tissue, cancer of the urethra, cancer of the penis, squamous cell, prostate cancer, chronic or acute leukemia, lymphocytic lymphomas, cancer of the bladder, cancer of the kidney or ureter, renal cell carcinoma, carcinoma of the renal pelvis, neoplasms of the central nervous system (CNS), primary CNS lymphoma, spinal axis tumors, brain, pituitary adenoma, or a combination of one or more of the foregoing cancers.

In a more preferred embodiment cancer is selected a solid tumor, such as, but not limited to, breast, lung, colon, brain, prostate, stomach, pancreatic, ovarian, skin (melanoma), endocrine, uterine, testicular, and bladder.

The compounds of the present invention may also be useful in the treatment of additional disorders in which aberrant expression ligand/receptor interactions or activation or signalling events related to various protein tyrosine kinases, are involved. Such disorders may include those of neuronal, glial, astrocytal, hypothalamic, and other glandular, macrophagal, epithelial, stromal, and blastocoelic nature in which aberrant function, expression, activation or signalling of the erbB tyrosine kinases are involved. In addition, the compounds of the present invention may have therapeutic utility in inflammatory, angiogenic and immunologic disorders

involving both identified and as yet unidentified tyrosine kinases that are inhibited by the compounds of the present invention.

The *in vitro* activity of the compounds of formula 1 may be determined by the following procedure. More particularly, the following assay provides a method to determine whether compounds of the formula 1 inhibit the tyrosine kinase activity of the catalytic construct FAK(410-689). The assay is an ELISA-based format, measuring the inhibition of poly-glu-tyr phosphorylation by FAK(410-689).

The assay protocol has three parts:

I. Purification and cleavage of His-FAK(410-689)

II. FAK410-689 (a.k.a. FAKcd) Activation

III. FAKcd Kinase ELISA

Materials:

-Ni-NTA agarose (Qiagen)

-XK-16 column (Amersham-Pharmacia)

-300 mM Imidizole

-Superdex 200 HiLoad 16/60 prep grade column (Amersham Biotech.)

-Antibody: Anti-Phosphotyrosine HRP-Conjugated Py20 (Transduction labs).

-FAKcd: Purified and activated in house

-TMB Microwell Peroxidase Substrate (Oncogene Research Products #CL07)

-BSA: Sigma #A3294

-Tween-20: Sigma #P1379

-DMSO: Sigma #D-5879

-D-PBS: Gibco #14190-037.

Reagents for Purification:

-Buffer A: 50mM HEPES pH 7.0,
500mM NaCl,
0.1mM TCEP
CompleteTM protease inhibitor cocktail tablets (Roche)

-Buffer B: 25mM HEPES pH 7.0,
400mM NaCl
0.1mM TCEP.

-Buffer C: 10mM HEPES pH 7.5,
200mM Ammonium Sulfate
0.1mM TCEP.

Reagents for Activation

-FAK(410-689): 3 tubes of frozen aliquots at 150ul/tube for a total of 450ul at 1.48 mg/ml (660ug)

-His-Src(249-524): ~0.74 mg/ml stock in 10mM HEPES, 200mM (NH4)2SO4

-Src reaction buffer (Upstate Biotech):

100 mM Tris-HCl pH7.2,

125mM $MgCl_2$,

25 mM $MnCl_2$,

2mM EDTA,

250 uM $Na_3VO_4$,

2 mM DTT

-Mn2+/ATP cocktail (Upstate Biotech)

75mM $MnCl_2$

500 uM ATP

20mM MOPS pH 7.2

1mM $Na_3VO_4$

25mM α-glycerol phosphate

5mM EGTA

1mM DTT

-ATP: 150mM stock

-$MgCl_2$: 1 M Stock

-DTT: 1M stock

Reagents for FAKcd Kinase ELISA

-Phosphorylation Buffer:

50mM HEPES, pH 7.5,

125mM NaCl,

48mM $MgCl_2$

-Wash Buffer: TBS + 0.1% Tween-20.

-Blocking Buffer:

Tris Buffer Saline,

3% BSA,

0.05% Tween-20, filtered.

-Plate Coating Buffer:

50mg/ml Poly-Glu-Tyr (Sigma #P0275) in Phosphate buffer Saline (DPBS).

-ATP: 0.1M ATP in $H_2O$ or HEPES, pH7.

Note: ATP Assay Buffer:

Make up as 75 uM ATP in PBS, so that 80 ul in

120 ul reaction volume=50uM final ATP concentration.

I. Purification of His-FAKcd(410-689)

1. Resuspend 130 g baculovirus cell paste containing the over expressed His-FAKcd410-689 recombinant protein in 3 volumes (400ml) of Buffer A,
2. Lyse cells with one pass on a microfluidizer
3. Remove cell debris by centrifugation at 4OC for 35 minutes at 14,000 rpm in a Sorval SLA-1500 rotor.
4. Transfer the supernatant to a clean tube and add 6.0 ml of Ni-NTA agarose (Qiagen)
5. Incubate the suspension with gentle rocking at 4O°C for 1 hour
6. Centrifuge suspension at 700 x g in a swinging bucket rotor.
7. Discard the supernatant and resuspend the agarose beads in 20.0 ml of Buffer A
8. Transfer the beads to an XK-16 column (Amersham-Pharmacia) connected to a FPLCTM.
9. Wash the agarose-beads with 5 column volumes of Buffer A and elute off the column with a step gradient of Buffer A containing 300mM Imidizole.
10. Perform a buffer exchange of the eluted fractions into Buffer B
11. Following buffer exchange, pool the fractions and add thrombin at a 1:300 (w/w) ratio and incubated overnight at 13°C to remove the N-terminal His-tag (His-FAK410-698 → FAK410-689 (a.k.a. FAKcd)).
12. Add the reaction mixture back onto the Ni-NTA column equilibrated with Buffer A and collect the flow-through.
13. Concentrate the flow-through down to 1.7 ml and load directly onto a Superdex 200 HiLoad 16/60 prep grade column equilibrated with Buffer C. The desired protein elutes between 85 - 95 ml.
14. Aliquot the FAKcd protein and store frozen at –80°C

II. FAK activation

1. To 450ul of FAK(410-689) at 1.48 mg/ml (660ug) add the following:

30ul of 0.037 mg/ml (1uM) His-Src(249-524)

30ul of 7.5 mM ATP

12ul of 20 mM $MgCl_2$

10ul Mn2+/ATP cocktail (UpState Biotech.)

4ul of 6.7mM DTT

60ul Src Reaction Buffer (UpState Biotech.)

2. Incubate Reaction for at least 3 hours at room temperature

At time $t_0$, almost all of the FAK(410-689) is singly phosphorylated. The second phosphorylation is slow. At $t_{120}$ (t = 120 minutes), add 10ul of 150 mM ATP.

$T_0$ = (Start) 90% singly phosphorylated FAK(410-689) (1 PO4)

$T_{43}$ = (43 min) 65% singly phosphorylated (1 PO4), 35% doubly phosphorylated (2 PO4)

$T_{90}$ = (90 min) 45% 1 PO4, 55% 2 PO4

$T_{150}$ = 15% 1 PO4, 85% 2 PO4

$T_{210}$ = <10% 1 PO4, >90% 2 PO4 desalted sample

3. Add 180 ul aliquots of the desalted material to NiNTA spin column and incubate on spin column

4. Spin at 10k rpm (microfuge), for 5 min to isolate and collect flow through (Activated FAK(410-689)) and remove His-Src (captured on column)

III. FAKcd Kinase ELISA

1. Coat 96-well Nunc MaxiSorp plates with poly-glu-tyr (pGT) at 10 ug/well: Prepare 10 ug/ml of pGT in PBS and aliquot 100 ul/well. Incubate the plates at 37°C overnight, aspirate the supernatant, wash the plates 3 times with Wash Buffer, and flick to dry before storing at 4°C.
2. Prepare compound stock solutions of 2.5 mM in 100% DMSO. The stocks are subsequently diluted to 60X of the final concentration in 100% DMSO, and diluted 1:5 in Kinase Phosphorylation Buffer.
3. Prepare a 75 uM working ATP solution in Kinase phosphorylation buffer. Add 80 ul to each well for a final ATP concentration of 50 uM.
4. Transfer 10 ul of the diluted compounds (0.5log serial dilutions) to each well of the pGT assay plate, running each compound in triplicates on the same plate.
5. Dilute on ice, FAKcd protein to 1:1000 in Kinase Phosphorylation Buffer. Dispense 30 ul per well.
6. Note: Linearity and the appropriate dilution must be pre-determined for each batch of protein. The enzyme concentration selected should be such that quantitation of the assay signal will be approximately 0.8-1.0 at $OD_{450}$, and in the linear range of the reaction rate.
7. Prepare both a No ATP control (noise) and a No Compound Control (Signal):
8. (Noise) One blank row of wells receives 10 ul of 1:5 diluted compounds in DMSO, 80ul of Phosphorylation buffer (minus ATP), and 30 ul FAKcd solution.
9. (Signal) Control wells receive 10 ul of 1:5 diluted DMSO (minus Compound) in Kinase phosphorylation buffer, 80 ul of 75 uM ATP, and 30 ul of 1:1000 FAKcd enzyme.
10. Incubate reaction at room temperature for 15 minutes with gentle shaking on a plate shaker.
11. Terminate the reaction by aspirating off the reaction mixture and washing 3 times with wash buffer.

12. Dilute phospho-tyrosine HRP-conjugated (pY20HRP) antibody to 0.250ug/ml (1:1000 of Stock) in blocking buffer. Dispense 100 ul per well, and incubate with shaking for 30min. at R.T.
13. Aspirate the supernatant and wash the plate 3 times with wash buffer.
14. Add 100 ul per well of room temperature TMB solution to initiate color development. Color development is terminated after approximately 15-30 sec. by the addition of 100ul of 0.09M $H_2SO_4$ per well.
15. The signal is quantitated by measurement of absorbance at 450nm on the BioRad microplate reader or a microplate reader capable of reading at $OD_{450}$.
16. Inhibition of tyrosine kinase activity would result in a reduced absorbance signal. The signal is typically 0.8-1.0 OD units. The values are reported as $IC_{50s}$, uM concentration.

FAK Inducible cell-based ELISA: Final Protocol

Materials:

Reacti-Bind Goat Anti-Rabbit Plates 96-well (Pierce Product#15135ZZ @115.00 USD)

FAKpY397 rabbit polyclonal antibody (Biosource #44624 @315.00 USD)

ChromePure Rabbit IgG, whole molecule (Jackson Laboratories #001-000-003 @60/25mg USD)

UBI αFAK clone 2A7 mouse monoclonal antibody (Upstate#05-182 @ 289.00 USD)

Peroxidase-conjugated AffiniPure Goat Anti-Mouse IgG (Jackson Labs #115-035-146 @95/1.5ml USD)

SuperBlock TBS (Pierce Product#37535ZZ @99 USD)

Bovine Serum Albumin (Sigma #A-9647 @117.95/100 g USD)

TMB Peroxidase substrate (Oncogene Research Products #CL07-100ml @40.00 USD)

$Na_3VO_4$ Sodium Orthovanadate (Sigma #S6508 @43.95/50g USD)

MTT substrate (Sigma # M-2128 @25.95/500mg USD)

Growth Media: DMEM+10%FBS, P/S, Glu, 750 ug/ml Zeocin and 50 ug/ml Hygromycin (Zeocin InVitrogen #R250-05 @ 725 USD and Hygromycon InVitrogen #R220-05 @ 150 USD)

Mifepristone InVitrogen # H110-01 @ 125 USD

CompleteTM EDTA-free Protease Inhibitor pellet Boehringer Mannheim #1873580

FAK cell-based Protocol for selectivity of kinase-dependent phosphoFAKY397

Procedure

An inducible FAK cell-based assay in ELISA format for the screening of chemical matter to identify tyrosine kinase specific inhibitors was developed. The cell-based assay exploits the

mechanism of the GeneSwitchTM system (InVitrogen) to exogenously control the expression and phosphorylation of FAK and the kinase-dependent autophosphorylation site at residue Y397.

Inhibition of the kinase-dependent autophosphorylation at Y397 results in a reduced absorbance signal at $OD_{450}$. The signal is typically 0.9 to 1.5 $OD_{450}$ units with the noise falling in the range of 0.08 to 0.1 $OD_{450}$ units. The values are reported as $IC_{50}$s, uM concentration.

On day 1, grow A431•FAKwt in T175 flasks. On the day prior to running the FAK cell-assay, seed A431•FAKwt cells in growth media on 96-well U-bottom plates. Allow cells to sit at 37°C, 5% $CO_2$ for 6 to 8 hours prior to FAK induction. Prepare Mifepristone stock solution of 10 uM in 100 % Ethanol. The stock solution is subsequently diluted to 10 X of the final concentration in Growth Media. Transfer 10 ul of this dilution (final concentration of 0.1 nM Mifepristone) into each well. Allow cells to sit at 37°C, 5% $CO_2$ overnight (12 to 16 hours). Also, prepare control wells without Mifepristone induction of FAK expression and phosphorylation.

On day 2, coat Goat Anti-Rabbit plate(s) with 3.5 ug/ml of phosphospecific FAKpY397 polyclonal antibody prepared in SuperBlock TBS buffer, and allow plate(s) to shake on a plate shaker at room temperature for 2 hours. Optionally, control wells may be coated with 3.5 ug/ml of control Capture antibody (Whole Rabbit IgG molecules) prepared in SuperBlock TBS. Wash off excess FAKpY397 antibody 3 times using buffer. Block Anti-FAKpY397 coated plate(s) with 200 ul per well of 3%BSA/0.5%Tween Blocking buffer for 1 hour at room temperature on the plate shaker. While the plate(s) are blocking, prepare compound stock solutions of 5 mM in 100 % DMSO. The stock solutions are subsequently serially diluted to 100X of the final concentration in 100% DMSO. Make a 1:10 dilution using the 100X solution into growth media and transfer 10 ul of the appropriate compound dilutions to each well containing *either* the FAK induced or uninduced control A431 cells for 30 minutes at 37°C, 5% $CO_2$. Prepare RIPA lysis buffer (50 mM Tris-HCl, pH7.4, 1% NP-40, 0.25% Na-deoxycholate, 150 mM NaCl, 1 mM EDTA, 1 mM Na3VO4, 1 mM NaF, and one CompleteTM EDTA-free protease inhibitor pellet per 50 ml solution). At the end of 30 minutes compound treatment, wash off compound 3 times using TBS-T wash buffer. Lyse cells with 100 ul/well of RIPA buffer.

To the coated plate, remove blocking buffer and wash 3 times using TBS-T wash buffer. Using a 96-well automated microdispenser, transfer 100 ul of whole cell-lysate (from step 6) to the Goat Anti-Rabbit FAKpY397 coated plate(s) to capture phosphoFAKY397 proteins. Shake at room temperature for 2 hours. Wash off unbound proteins 3 times using TBS-T wash buffer. Prepare 0.5 ug/ml (1:2000 dilution) of UBI αFAK detection antibody in 3%BSA/0.5% Tween blocking buffer. Dispense 100 ul of UBI αFAK solution per well and shake for 30 minutes at room temperature. Wash off excess UBI αFAK antibody 3 times using TBS-T wash buffer. Prepare 0.08 ug/ml (1:5000 dilution) of secondary Anti-Mouse Peroxidase (Anti-2MHRP) conjugated antibody. Dispense 100 ul per well of the Anti-2MHRP solution and shake for 30 minutes at room temperature. Wash off excess Anti-2MHRP antibody 3 times using TBS-T

wash buffer. Add 100 ul per well of room temperature TMB substrate solution to allow for color development. Terminate the TMB reaction with 100 ul per well of TMB stop solution (0.09M $H_2SO_4$) and quantitate the signal by measurement of absorbance at 450 nm on the BioRad microplate reader.

Additional FAK cell assays are hereby incorporated by reference from Pfizer Attorney Docket No. PC11699 entitled "INDUCIBLE FOCAL ADHESION KINASE CELL ASSAY".

Administration of the compounds of the present invention (hereinafter the "active compound(s)") can be effected by any method that enables delivery of the compounds to the site of action. These methods include oral routes, intraduodenal routes, parenteral injection (including intravenous, subcutaneous, intramuscular, intravascular or infusion), topical, and rectal administration.

The amount of the active compound administered will be dependent on the subject being treated, the severity of the disorder or condition, the rate of administration, the disposition of the compound and the discretion of the prescribing physician. However, an effective dosage is in the range of about 0.001 to about 100 mg per kg body weight per day, preferably about 1 to about 35 mg/kg/day, in single or divided doses. For a 70 kg human, this would amount to about 0.05 to about 7 g/day, preferably about 0.2 to about 2.5 g/day. In some instances, dosage levels below the lower limit of the aforesaid range may be more than adequate, while in other cases still larger doses may be employed without causing any harmful side effect, provided that such larger doses are first divided into several small doses for administration throughout the day.

The active compound may be applied as a sole therapy or may involve one or more other anti-tumour substances, for example those selected from, for example, mitotic inhibitors, for example vinblastine; alkylating agents, for example cis-platin, carboplatin and cyclophosphamide; anti-metabolites, for example 5-fluorouracil, cytosine arabinoside and hydroxyurea, or, for example, one of the preferred anti-metabolites disclosed in European Patent Application No. 239362 such as N-(5-[N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-methylamino]-2-thenoyl)-L-glutamic acid; growth factor inhibitors; cell cycle inhibitors; intercalating antibiotics, for example adriamycin and bleomycin; enzymes, for example interferon; and anti-hormones, for example anti-estrogens such as Nolvadex™ (tamoxifen) or, for example anti-androgens such as Casodex™ (4'-cyano-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methyl-3'-(trifluoromethyl)propionanilide). Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate dosing of the individual components of the treatment.

The pharmaceutical composition may, for example, be in a form suitable for oral administration as a tablet, capsule, pill, powder, sustained release formulations, solution, suspension, for parenteral injection as a sterile solution, suspension or emulsion, for topical administration as an ointment or cream or for rectal administration as a suppository. The pharmaceutical composition may be in unit dosage forms suitable for single administration of

precise dosages. The pharmaceutical composition will include a conventional pharmaceutical carrier or excipient and a compound according to the invention as an active ingredient. In addition, it may include other medicinal or pharmaceutical agents, carriers, adjuvants, etc.

Exemplary parenteral administration forms include solutions or suspensions of active compounds in sterile aqueous solutions, for example, aqueous propylene glycol or dextrose solutions. Such dosage forms can be suitably buffered, if desired.

Suitable pharmaceutical carriers include inert diluents or fillers, water and various organic solvents. The pharmaceutical compositions may, if desired, contain additional ingredients such as flavorings, binders, excipients and the like. Thus for oral administration, tablets containing various excipients, such as citric acid may be employed together with various disintegrants such as starch, alginic acid and certain complex silicates and with binding agents such as sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often useful for tableting purposes. Solid compositions of a similar type may also be employed in soft and hard filled gelatin capsules. Preferred materials, therefor, include lactose or milk sugar and high molecular weight polyethylene glycols. When aqueous suspensions or elixirs are desired for oral administration the active compound therein may be combined with various sweetening or flavoring agents, coloring matters or dyes and, if desired, emulsifying agents or suspending agents, together with diluents such as water, ethanol, propylene glycol, glycerin, or combinations thereof.

Methods of preparing various pharmaceutical compositions with a specific amount of active compound are known, or will be apparent, to those skilled in this art. For examples, see Remington's Pharmaceutical Sciences, Mack Publishing Company, Easter, Pa., 15th Edition (1975).

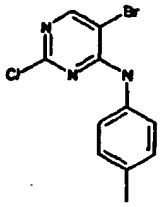
The examples and preparations provided below further illustrate and exemplify the compounds of the present invention and methods of preparing such compounds. It is to be understood that the scope of the present invention is not limited in any way by the scope of the following examples and preparations. In the following examples molecules with a single chiral center, unless otherwise noted, exist as a racemic mixture. Those molecules with two or more chiral centers, unless otherwise noted, exist as a racemic mixture of diastereomers. Single enantiomers/diastereomers may be obtained by methods known to those skilled in the art.

General Methods

Method A

General method for introduction of a group at C-4

(5-Bromo-2-chloro-pyrimidin-4-yl)-p-tolyl-amine



A mixture of 5-Bromo-2,4-dichloropyrimidine (5.00 g, 22.0 mmol), di-isopropyl ethylamine (3.91 mL, 22.4 mmol) and p-toluidine (2.40 g, 22.4 mmol) in n-butanol (50.0 mL) was heated to 105°C under nitrogen for three hours. The reaction was allowed to cool to room temperature. The resulting mixture was poured into ethyl acetate and extracted with 1 N NaOH. The aqueous layer was removed and the organic layer was washed with water, dried over magnesium sulfate, filtered and evaporated under reduced pressured. To the resulting oily residue, diethyl ether was added and the mixture was then cooled to 0° C. HCl (4.0 M in dioxane) was added dropwise. The resulting white solid was filtered and dried. The salt was suspended in a mixture of water and ethyl acetate. The pH of the aqueous layer was then adjusted to 9 with 1N NaOH and extracted. The aqueous layer was further extracted with ethyl acetate. The organic layers were combined, dried over magnesium sulfate, filtered and evaporated under reduced pressure to afford 5-Bromo-2-chloro-pyrimidin-4-yl)-p-tolyl-amine (3.62 g, 55%) as a white solid: $C_{11}H_8BrClN_3$. GC/MS: ret. Time = 4.65 min, m/z 296/298/300; g.l.c. purity: 100%; TLC $R_f$ 0.58 (20% Ethyl acetate/hexanes); $^1$H NMR ($d_6$-DMSO) δ 9.21 (s, 1H), 8.39 (s, 1H), 7.35 (d, *J* = *8.4 Hz*, 2 H), 7.16 (d, *J* = *8.4 Hz*, 2 H), 2.27 (s, 3 H) ppm.

Method B

General method for introduction of a group at C-4

(2-Chloro-5-fluoro-pyrimidin-4-yl)-pyridin-2-ylmethyl-amine

To a solution of 5-fluoro-2,4-dichloropyrimidine (1.5 g; 9 mmol) in THF (25 mL) was added triethylamine (1.1 eq), followed by dropwise addition of 2-(aminomethyl)pyridine (0.973 g; 1 eq). After stirring for one hour the reaction was concentrated and taken up in ethyl acetate, washed with saturated $NaHCO_3$, dried over $Na_2SO_4$, and the solvent removed. The resulting solid was re-crystallized from ethyl acetate and hexanes as a white solid (1.74g; 81%): $^1$H NMR ($CDCl_3$, 400 MHz) δ 4.84 (d, *J* = 4.7 Hz, 2H), 7.07 (bs, 1H), 7.35 (t, *J* = 5.1 Hz, 1H), 7.44 (d, *J* = 7.8, 1H), 7.82 (t, *J* = 7.6, 1H), 7.95 (d, *J* = 2.5 Hz, 1H), 8.63 (d, *J* = 5.0 Hz, 1H); HPLC ret. Time: 4.228 min. LRMS (M+): 239.0, 241.0.

Method C

General method for introduction of a group at C-4

Using method B, replace the THF solvent with 1,4-dioxane as solvent.

Method D

General method for introduction of a group at C-4

5-Fluoro-$N^2$-(1H-indazol-5-yl)-$N^4$-pyridin-2-ylmethyl-pyrimidine-2,4-diamine

(2-Chloro-5-fluoro-pyrimidin-4-yl)-pyridin-2-ylmethyl-amine (100 mg; 0.4 mmol) and 5-aminoindazole (56 mg; 1 eq) were combined and heated at 160° C for 30 minutes. After cooling to room temperature, methanol (1mL) was added and stirred for 15 minutes, followed by filtration gave the product as a brown solid (29 mg; 21%): $^1$H NMR ($CD_3OD$, 400 MHz) δ 4.80 (s, 2H), 7.34 (m, 3H), 7.43 (d, *J* = 7.8 Hz, 1H), 7.8 (m, 2H), 7.87 (s, 1H), 7.90 (s, 1H), 8.54 (d, *J* = 5 Hz, 1H); HPLC ret. time: 3.916 min. LRMS (M+): 336.1.

Method E

General method for introduction of C-2 Group

5-(5-Bromo-4-phenethylamino-pyrimidin-2-ylamino)-1,3-dihydro-indol-2-one

153 mg (0.490 mmol) (5-Bromo-2-chloro-pyrimidin-4-yl)-phenethyl-amine was taken into 0.5 mL 1,4 dioxane with 0.14 mL (1.00 mmol) diisopropylethylamine and 80 mg (0.539 mmol) 5-amino-1,3-dihydro-indol-2-one. The reaction was allowed to heat to 110° C for sixteen hours. The resulting brown glass was taken into 92.3:7:0.7 $CHCl_3$:$CH_3OH$:$NH_4OH$ and washed with 1 N sodium hydroxide. The organic layer was dried over magnesium sulfate and evaporated directly onto silica gel. This adsorbed compound was purified via column chromatography (97.8:2:0.2 $CHCl_3$:$CH_3OH$:$NH_4OH$) over silica to isolate the major product. The title compound was isolated as a white solid. $C_{20}H_{18}BrN_5O$: MS: 424.2/426.2 (MH+); $^1$H NMR ($D_6$-DMSO) 10.20 (s, 1 H), 9.01 (s, 1 H), 7.93 (s, 1 H), 7.52 (s, 1 H), 7.44 (d, *J* = *8.4 Hz*, 1 H), 7.28 - 7.16 (m, 5 H), 6.97 (m, 1 H), 6.65 (d, *J* = *8.3 Hz*, 1 H), 3.56 (m, 2 H), 3.31 (s, 2 H), 2.82 (t, *J* = *7.9 Hz*, 2 H) ppm.

Method F

General method for introducing both C-2 and C-4 amines ("One Pot Method")

4-(5-[5-Bromo-4-(4-trifluoromethyl-benzylamino)-pyrimidin-2-ylamino]-1H-indol-3-yl)-3,6-dihydro-2H-pyridine-1-carboxylic acid tert-butyl ester

To a stirred solution of 5-bromo-2,4-dichloropyrimidine (0.222 g, 0.98 mmol) in THF (3 mL) under nitrogen was added triethylamine (0.42 mL, 3 mmol) followed by dropwise addition of p-trifluoromethylbenzyl amine (0.175 g,1 mmol). After three hours the THF was removed under reduced pressure. To the resulting residue was added dioxane (1 mL) followed by 4-(5-Amino-1H-indol-3-yl)-3,6-dihydro-2H-pyridine-1-carboxylic acid tert-butyl ester (0.345 g 1.1 mmol). The mixture was stirred under nitrogen and then heated to 110° C for sixteen hours. The reaction was cooled and was then dissolved in a solution of 5% methanol-dichloromethane and extracted with 1 N NaOH. The organic and aqueous layers were

separated and the aqueous layer was further extracted with additional 5% methanol-dichloromethane. The organic layers were combined, washed with brine, dried over magnesium sulfate, filtered and evaporated under reduced pressure. The resulting residue was purified by silica gel chromotography (30% ethyl acetate in hexanes) to give 4-{5-[5-Bromo-4-(4-trifluoromethyl-benzylamino)-pyrimidin-2-ylamino]-1H-indol-3-yl}-3,6-dihydro-2H-pyridine-1-carboxylic acid tert-butyl ester (150 mg, 23%):

Method G

TFA General de-protection Method

5-Bromo-N2-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-$N^4$-(4-trifluoromethyl-benzyl)-pyrimidine-2,4-diamine trifluoro acetate salt

To a stirred solution of 4-{5-[5-Bromo-4-(4-trifluoromethyl-benzylamino)-pyrimidin-2-ylamino]-1H-indol-3-yl}-3,6-dihydro-2H-pyridine-1-carboxylic acid tert-butyl ester (0.15 g) in dichloromethane (2 mL) at 0° C under nitrogen was added trifluoroacetic acid (4 mL). The cooling bath was removed and the reaction mixture was stirred for four hours. The reaction was concentrated under reduced pressure. To the resulting residue was added ethyl acetate (2 mL) followed by concentrating to an oily residue. The ethyl acetate concentration sequence was repeated three times. The resulting residue was suspended in ethyl acetate follow by addition of diethyl ether to precipitate 5-Bromo-N2-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-$N^4$-(4-trifluoromethyl-benzyl)-pyrimidine-2,4-diamine trifluoroacetate salt (0.129 g, 86%) as a white solid: $C_{25}H_{22}BrF_3N_6$. MS: 542.9/544.7 (MH+). $^1$H NMR ($D_6$-DMSO) δ 11.31 (s, 1 H), 8.82 (s, 2 H), 8.08 (s, 1 H), 7.88 (s, 1 H), 7.53 (s, 3 H), 7.36 (s, 2 H), 7.28 (d, *J* = *8.3 Hz*, 1 H), 7.16 (d, *J* = *8.3 Hz*, 1 H), 6.05 (bs, 1 H), 4.58 (s, 2 H), 3.75-3.65 (bs, 2 H), 3.35-3.25 (bs, 2 H), 2.70-2.60 (bs, 2 H) ppm

Method H

HCl General de-protection Method

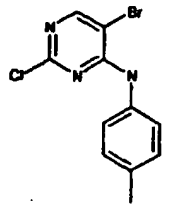
5-Bromo-N2-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-$N^4$-p-tolyl-pyrimidine-2,4-diamine hydrochloride salt

To a stirred solution of 4-[5-(5-Bromo-4-p-tolylamino-pyrimidin-2-ylamino)-1H-indol-3-yl]-3,6-dihydro-2H-pyridine-1-carboxylic acid tert-butyl ester (0.1 g, 0.174 mmol) and methanol (3 mL) cooled to 0° C under nitrogen was added HCl in dioxane (0.2 mL of a 4 M solution). The cooling bath was removed and the reaction was allowed to stir for 6 hours. The mixture was concentrated under reduced pressure and the resultant residue was triturated with dichloromethane. The solid was filtered, washed with dichloromethane and dried to give 5-Bromo-N2-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-$N^4$-p-tolyl-pyrimidine-2,4-diamine hydrochloride salt (0.076 g, 85%) as a white solid: $C_{24}H_{23}BrN_6$. MS: 475.0/477.0 (MH+); $^1$H NMR ($D_6$-DMSO) δ 10.98 (s, 1 H), 9.01 (s, 1 H), 8.28 (s, 1 H), 8.12 (s, 1 H), 7.89 (s, 1 H), 7.50 - 7.58 (m, 3 H), 7.41 (d, *J* = *8.7 Hz*, 1 H), 7.29 (s, 1 H), 7.18 (d, *J* = *8.7 Hz*, 1 H), 7.03 (d, *J* = *8.3 Hz*, 2 H), 6.02 (s, 1 H), 4.03 (m, 2 H), 2.47 (m, 2 H), 2.35 (m, 2 H), 2.23 (s, 3 H) ppm.

Example 1

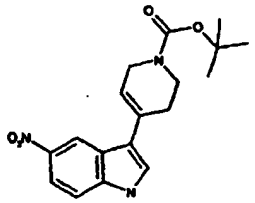
5-Bromo-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-$N^4$-p-tolyl-pyrimidine-2,4-diamine

A. 5-Bromo-2-chloro-pyrimidin-4-yl)-p-tolyl-amine



A mixture of 5-Bromo-2,4-dichloropyrimidine (5.00 g, 22.0 mmol), di-isopropyl ethylamine (3.91 mL, 22.4 mmol) and p-toluidine (2.40 g, 22.4 mmol) in n-butanol (50.0 mL) was heated to 105°C under nitrogen for three hours. The reaction was allowed to cool to room temperature. The resulting mixture was poured into ethyl acetate and extracted with 1 N NaOH. The aqueous layer was removed and the organic layer was washed with water, dried over magnesium sulfate, filtered and evaporated under reduced pressured. To the resulting oily residue, diethyl ether was added and the mixture was then cooled to 0° C. HCl (4.0 M in dioxane) was added dropwise. The resulting white solid was filtered and dried. The salt was suspended in a mixture of water and ethyl acetate. The pH of the aqueous layer was then adjusted to 9 with 1N NaOH and extracted. The aqueous layer was further extracted with ethyl acetate. The organic layers were combined, dried over magnesium sulfate, filtered and evaporated under reduced pressure to afford 5-Bromo-2-chloro-pyrimidin-4-yl)-p-tolyl-amine (3.62 g, 55%) as a white solid: $C_{11}H_9BrClN_3$. GC/MS: ret. Time = 4.65 min, m/z 296/298/300; g.l.c. purity: 100%; TLC $R_f$ 0.58 (20% Ethyl acetate/hexanes); $^1H$ NMR ($d_6$-DMSO) δ 9.21 (s, 1H), 8.39 (s, 1H), 7.35 (d, *J = 8.4 Hz*, 2 H), 7.16 (d, *J = 8.4 Hz*, 2 H), 2.27 (s, 3 H) ppm.

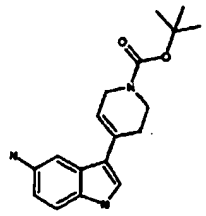
B. 4-(5-Nitro-1H-indol-3-yl)-3,6-dihydro-2H-pyridine-1-carboxylic acid tert-butyl ester



To 600 mL of HPLC-grade methanol was added 60.0 g (1.11 mol) sodium methoxide portion-wise. The resulting white slurry was allowed to stir for ten minutes before adding 30.0 g (185 mmol) 5-nitroindole. This allowed to stir for an additional ten minutes before adding 92.2 g (463 mmol) 4-Oxo-piperidine-1-carboxylic acid tert-butyl ester. After waiting ten minutes, the reaction temperature was ramped to 85° C which was maintained for thirty-two hours. The black reaction solution was cooled to 0° C and 250 mL distilled water was added

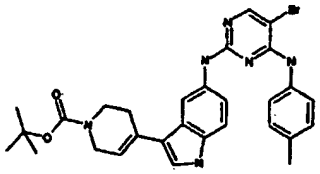
drop-wise under nitrogen via an equalizing pressure addition funnel. The methanol was removed under reduced pressure. To the aqueous residue was added 1.50 L dichloromethane. The organic layer was separated. The pH of the aqueous was adjusted to 9.00 using sodium hydroxide. Dichloromethane was added and the two layers were filtered through diatomaceous earth to alleviate emulsion. The organic layer was separated and combined with the original organic. The combined organic layers were dried over magnesium sulfate. Partial evaporation of the dried organics resulted in a yellow-orange slurry. Filtration of this solid followed by washing with 5:1 diethyl ether:dichloromethane afforded 49.98 g (146 mmol, 79%) of the title compound as a yellow solid. MS: 244.1 (M-Boc H+); TLC $R_f$: 0.31 (40% ethyl acetate/hexanes); $^1$H NMR ($D_6$-DMSO) δ 11.90 (s, 1H), 8.68 (s, 1H), 7.99 (d, *J = 8.8 Hz*, 1 H), 7.68 (s, 1 H), 7.53 (d, *J = 8.8 Hz*, 1H), 6.17 (s, 1H), 4.04 (m, 2 H), 3.54 (m, 1 H), 2.47 (m, 2H), 1.40 (s, 9 H) ppm.

C. 4-(5-Amino-1H-indol-3-yl)-3,6-dihydro-2H-pyridine-1-carboxylic acid tert-butyl ester



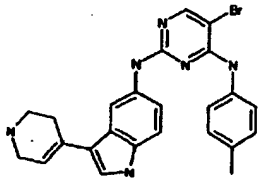
To a solution of 400 mL dioxane, 300 mL ethanol, and 200 mL distilled water was added ten grams of 4-(5-Nitro-1H-indol-3-yl)-3,6-dihydro-2H-pyridine-1-carboxylic acid tert-butyl ester. To this was added 8.13 g (146 mmol) powdered iron (0) and 6.23 g (116 mmol) ammonium chloride. The reaction was heated to 70° C under nitrogen with the iron eventually becoming a conglomerate around the magnetic stir bar. After three hours, the reaction was removed from the heating source allowed to cool to room temperature and filtered. The filtrate was evaporated under reduced pressure. The aqueous residue was partitioned with ethyl acetate, dried over magnesium sulfate and filtered. Evaporation of the filtrate afforded the title compound as a tan glassy foam which darkens upon exposure to air. $C_{18}H_{23}N_3O_2$: 8.57 g (27.3 mmol, 94%): MS 214.1 (M-Boc H+); TLC $R_f$: 0.18 (40% Ethyl acetate : hexanes); $^{13}$C NMR ($D_6$-DMSO) δ 154.6, 142.5, 131.3, 126.1, 123.4, 115.4, 114.9, 112.6, 112.5, 104.2, 79.3, 44.0, 43.8, 41.5, 28.8, 28.3 ppm; $^1$H NMR ($D_6$-DMSO) δ 10.71(s, 1H), 7.24 (s, 1H), 7.09 (d, *J = 8.4 Hz*, 1H), 7.04 (s, 1 H), 6.53 (d, *J = 8.4 Hz*, 1 H), 6.00 (s, 1H), 4.54 (s, 2H), 4.54 (m, 2 H), 4.05 (m, 2 H), 3.56 (m, 2 H), 2.51 (m, 2 H), 1.45 (s, 9 H) ppm.

D. 4-[5-(5-Bromo-4-p-tolylamino-pyrimidin-2-ylamino)-1H-indol-3-yl]-3,6-dihydro-2H-pyridine-1-carboxylic acid tert-butyl ester



2.32 g (7.77 mmol) (5-Bromo-2-chloro-pyrimidin-4-yl)-p-tolyl-amine was taken into 21.0 mL dioxane with 2.92 g (2.92 mmol) 4-(5-Amino-1H-indol-3-yl)-3,6-dihydro-2H-pyridine-1-carboxylic acid tert-butyl ester and 1.30 mL (9.32 mmol) triethyl amine. The reaction was heated to 100° C for sixteen hours. The reaction was allowed to cool to room temperature, and the dioxane was removed under reduced pressure. The brown residue was taken into ethyl acetate and 1 N sodium hydroxide mixture. Aqueous work-up gave approximately 3 g brown tar. This brown tar was purified to give 2.43 g (4.21 mmol, 54%) white solid. $C_{29}H_{31}BrN_6O_2$: MS: 575.0/577.0 (MH+); $^1$H NMR ($D_6$-DMSO) δ 11.00 (s, 1 H), 9.01 (s, 1 H), 8.28 (s, 1 H), 8.13 (s, 1 H), 7.93 (s, 1 H), 7.53 (d, *J = 8.3 Hz*, 2 H), 7.35 (s, 1 H), 7.34 (d, *J = 8.8 Hz*, 1 H), 7.19 (d, *J = 8.8 Hz*, 1 H), 7.02 (d, *J = 8.3 Hz*, 2 H), 5.93 (s, 1 H), 3.89 (m, 2 H), 3.50 (m, 2 H), 3.14 (m, 2 H), 2.21 (s, 3 H), 1.39 (s, 9 H) ppm; TLC $R_f$ 0.32 (40% ethyl acetate in hexanes).

E. 5-Bromo-N$^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-N$^4$-p-tolyl-pyrimidine-2,4-diamine

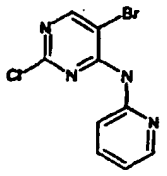


To a stirred solution of 4-[5-(5-Bromo-4-p-tolylamino-pyrimidin-2-ylamino)-1H-indol-3-yl]-3,6-dihydro-2H-pyridine-1-carboxylic acid tert-butyl ester (0.1 g, 0.174 mmol) and methanol (3 mL) cooled to 0° C under nitrogen was added HCl in dioxane (0.2 mL of a 4 M solution). The cooling bath was removed and the reaction was allowed to stir for 6 hours. The mixture was concentrated under reduced pressure and the resultant residue was triturated with dichloromethane. The solid was filtered, washed with dichloromethane and dried to give 5-Bromo-N2-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-N$^4$-p-tolyl-pyrimidine-2,4-diamine hydrochloride salt (0.076 g, 85%) as a white solid: $C_{24}H_{23}BrN_6$. MS: 475.0/477.0 (MH+); $^1$H NMR ($D_6$-DMSO) δ 10.98 (s, 1 H), 9.01 (s, 1 H), 8.28 (s, 1 H), 8.12 (s, 1 H), 7.89 (s, 1 H), 7.50 - 7.58 (m, 3 H), 7.41 (d, *J = 8.7 Hz*, 1 H), 7.29 (s, 1 H), 7.18 (d, *J = 8.7 Hz*, 1 H), 7.03 (d, *J = 8.3 Hz*, 2 H), 6.02 (s, 1 H), 4.03 (m, 2 H), 2.47 (m, 2 H), 2.35 (m, 2 H), 2.23 (s, 3 H) ppm.

Example 2

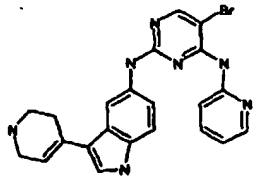
5-Bromo-N⁴-pyridin-2-yl-N2-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine

A. (5-Bromo-2-chloro-pyrimidin-4-yl)-pyridin-2-yl-amine



The title compound was prepared from 2-aminopyridine in a 10% yield as a yellow solid in a manner similar to Example 1A. $C_9H_6BrClN_4$. GC/MS: ret. time = 4.19 min. m/z 284/286/288, 205/207, 169, 78; $^1$H NMR ($D_6$-DMSO) δ 9.06 (bs, 1 H), 8.57 (s, 1 H), 8.38 (d, *J* = 4.6 Hz, 1 H), 7.93-7.86 (m, 2 H), 7.20 (dd, *J* = 4.6, 6.2 Hz, 1 H) ppm.

B. 5-Bromo-N⁴-pyridin-2-yl-N²-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine

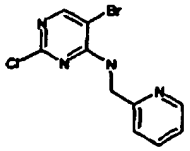


The title compound was made in a manner similar to Examples 1D and 1E. The compound was isolated as its HCl salt in a 29% yield as a yellow solid. $C_{22}H_{20}BrN_7$. MS: 462.1/464.1 (MH+). $^1$H NMR ($CD_3OD$) δ 8.37 (s, 1 H), 8.2 - 7.8 (m, 4 H), 7.53 (m, 2 H), 7.29 (m, 2 H), 6.18 (bs, 1 H), 4.93 - 4.80 (m, 2 H), 3.87 - 3.48 (m, 2 H), 3.00 - 2.80 (m, 2 H) ppm.

Example 3

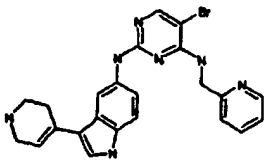
5-Bromo-N⁴-pyridin-2-ylmethyl-N²-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine

A. (5-Bromo-2-chloro-pyrimidin-4-yl)-pyridin-2-ylmethyl-amine



The title compound was made in 82% yield as a yellow oil that solidifies on standing. $C_{10}H_8BrClN_4$. GC/MS ret. time = 4.67 min. m/z 298/300/302, 219/221, 107. $^1$H NMR ($CDCl_3$) δ 8.64 (d, *J* = 4.7 Hz, 1 H), 8.19 (s, 1 H), 7.78 (t, *J* = 7.8 Hz, 1 H), 7.41 - 7.29 (m, 3H), 4.82 (d, *J* = 4.7 Hz, 2 H) ppm.

B. 5-Bromo-$N^4$-pyridin-2-ylmethyl-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine

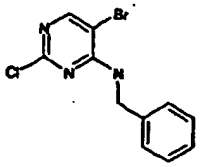


The title compound was made in a manner similar to Example 1D and 1E in 14% yield isolated as a free based white solid. $C_{23}H_{22}BrN_7$. MS: 447.0/449.0 (MH+), $^1$H NMR ($D_6$-DMSO) δ 10.85 (s, 1 H), 8.91 (s, 1 H), 8.50 (s, 1 H), 8.01-8.00 (m, 2 H), 7.68 (t, *J* = 6.4 *Hz*, 1 H), 7.42 (t, *J* = 5.7 *Hz*, 1 H), 7.28 - 7.20 (m, 4 H), 7.09 (d, *J* = 8.3 *Hz*, 1 H), 6.07 (s, 1 H), 4.70 (d, *J* = 5.7 *Hz*, 2 H), 3.40 - 3.30 (m, 2 H), 2.90 - 2.87 (m, 2 H), 2.50 - 2.40 (m, 2 H) ppm.

Example 4

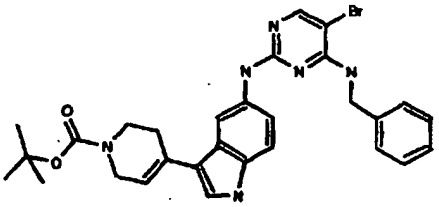
$N^4$-Benzyl-5-bromo-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine

A. Benzyl-(5-bromo-2-chloro-pyrimidin-4-yl)-amine



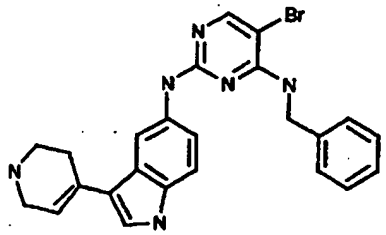
The title compound was synthesized in a manner similar to Example 1A. It was isolated in an 85% yield as a yellow solid. $C_{11}H_9BrClN_3$. MS 296.1/298.0 (MH+). $^1$H NMR ($CDCl_3$) δ 8.19 (s, 1 H), 7.45 - 7.30 (m, 5 H), 5.85 (bs, 1 H), 4.74 (d, *J* = 5.6 *Hz*, 2 H) ppm.

B. 4-[5-(4-Benzylamino-5-bromo-pyrimidin-2-ylamino)-1H-indol-3-yl]-3,6-dihydro-2H-pyridine-1-carboxylic acid tert-butyl ester



The title compound was made in a manner similar to Example 1D. It was isolated in a 65% yield after chromatography (30% EtOAc in hexanes) as a white solid. $C_{29}H_{31}BrN_6O_2$. MS: 575.0/576.8 (MH+). $^1$H NMR ($D_6$-DMSO) δ 10.95 (s, 1 H), 8.92 (s, 1 H), 8.14 (s, 1 H), 7.96 (s, 1 H), 7.48-7.14 (m, 9 H), 6.02 (s, 1 H), 4.61 (d, *J* = 6.2 *Hz*, 2 H), 4.01-3.98 (m, 2 H), 3.51-3.48 (m, 2 H), 2.47-2.45 (m, 2 H), 1.38 (s, 9H) ppm.

C. $N^4$-Benzyl-5-bromo-N2-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine

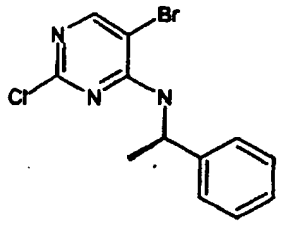


The title compound was synthesized by dissolving 4-[5-(4-Benzylamino-5-bromo-pyrimidin-2-ylamino)-1H-indol-3-yl]-3,6-dihydro-2H-pyridine-1-carboxylic acid tert-butyl ester into 5.00 mL dichloromethane and cooling to 0° C. To this was added 10.0 mL Trifluoroacetic acid. The red solution was allowed to slowly warm to room temperature and stir under N2 for two hours. 5.00 mL ethyl acetate was added. Filtration of the resulting precipitate gave the title compound as a white solid. $C_{24}H_{23}BrN_6$. MS: 475.0/476.8 (MH+). $^1$H NMR ($CD_3OD$) δ 11.05 (s, 1 H), 7.88 (s, 1 H), 7.81 (s, 1 H), 7.49 (s, 1 H), 7.45 (d, *J = 8.7Hz*, 1 H), 7.36-7.13 (m, 8 H), 6.15 (bs, 1 H), 4.64 (bs, 2 H), 3.90-3.80 (bs, 2 H), 3.49-3.43 (bs, 2 H), 2.85-2.83 (bs, 2H) ppm..

Example 5

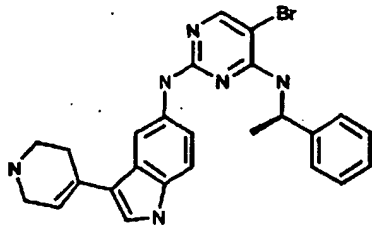
5-Bromo-N4-(1R-phenyl-ethyl)-N2-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine

A. (5-Bromo-2-chloro-pyrimidin-4-yl)-(1R-phenyl-ethyl)-amine



The title compound was made in a manner similar to Example 1A. It was isolated as an orange solid in a nearly quantitative yield. $C_{12}H_{11}BrClN_3$. MS: 312.1/314.1 (MH+). $^1$H NMR ($CDCl_3$) δ 8.11 (s, 1 H), 7.37 - 7.14 (m, 5 H), 5.71 (d, *J = 7.4 Hz*, 1 H), 5.35 (dt, *J = 7.4, 6.7 Hz*, 1 H), 1.60 (d, *J = 6.7 Hz*, 3 H) ppm.

B. 5-Bromo-N4-(1R-phenyl-ethyl)-N2-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine

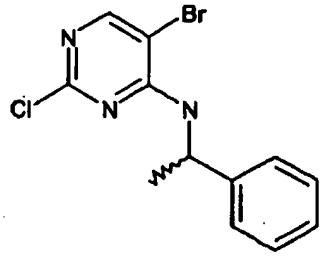


The title compound was made in a manner similar to Example 1D and deprotected similarly to Example 4C to give the desired material as its TFA salt in a 18% yield (tan solid). $C_{25}H_{25}BrN_6$. MS 489.0/491.1 (MH+); $^1$H NMR ($D_6$-DMSO) δ 11.37 (s, 1 H), 8.91 (s, 1 H), 8.11 (s, 1 H), 7.94 (s, 1 H), 7.57 (s, 1 H), 7.40 (d, *J* = *8.8 Hz*, 1 H), 7.30 – 7.22 (m, 7 H), 6.12 (s, 1 H), 4.06 (bs, 1 H), 3.77 – 3.75 (bs, 2 H), 3.38-3.36 (bs, 2 H), 2.76-2.75 (bs, 2 H), 1.57 (d, *J* = *6.8 Hz*, 3 H) ppm.

Example 6

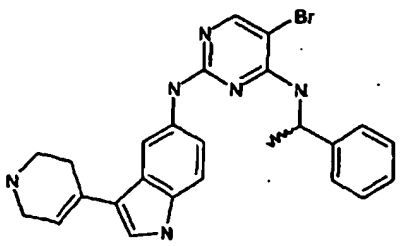
5-Bromo-$N^4$-(1*rac*-phenyl-ethyl)-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine

A. (5-Bromo-2-chloro-pyrimidin-4-yl)-(1*rac*-phenyl-ethyl)-amine



The title compound was made in a manner similar to Example 1A. It was isolated as an orange solid in nearly quantitative yield. $C_{12}H_{11}BrClN_3$. MS: 312.1/314.1 (MH+). $^1$H NMR ($CDCl_3$) δ 8.11 (s, 1 H), 7.37 - 7.14 (m, 5 H), 5.71 (d, *J* = *7.4 Hz*, 1 H), 5.35 (dt, *J* = *7.4, 6.7 Hz*, 1 H), 1.60 (d, *J* = *6.7 Hz*, 3 H) ppm

B. 5-Bromo-N4-(1*rac*-phenyl-ethyl)-N2-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine

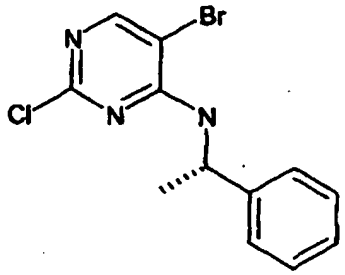


The title compound was made in a manner similar to Example 1D and deprotected similarly to Example 4C to give the desired material as its TFA salt in a 27% yield (tan solid). $C_{25}H_{25}BrN_6$. MS 489.0/491.1 (MH+); $^1$H NMR ($d_6$-DMSO) δ11.37 (s, 1 H), 8.91 (s, 1 H), 8.11 (s, 1 H), 7.94 (s, 1 H), 7.57 (s, 1 H), 7.40 (d, *J = 8.8 Hz*, 1 H), 7.30 – 7.22 (m, 7 H), 6.12 (s, 1 H), 4.06 (bs, 1 H), 3.77 – 3.75 (bs, 2 H), 3.38-3.36 (bs, 2 H), 2.76-2.75 (bs, 2 H), 1.57 (d, *J = 6.8 Hz*, 3 H) ppm.

Example 7

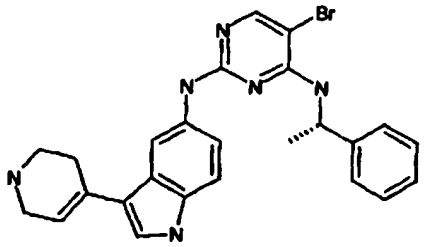
5-Bromo-N4-(1S-phenyl-ethyl)-N2-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine

A. (5-Bromo-2-chloro-pyrimidin-4-yl)-(1S-phenyl-ethyl)-amine



The title compound was made in a manner similar to Example 1A. It was isolated as an yellow solid in a 84% yield. $C_{12}H_{11}BrClN_3$. MS: 312.1/314.1 (MH+). $^1$H NMR ($CDCl_3$) d 8.11 (s, 1 H), 7.37 - 7.14 (m, 5 H), 5.71 (d, *J = 7.4 Hz*, 1 H), 5.35 (dt, *J = 7.4, 6.7 Hz*, 1 H), 1.60 (d, *J = 6.7 Hz*, 3 H) ppm

B. 5-Bromo-N4-(1S-phenyl-ethyl)-N2-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine

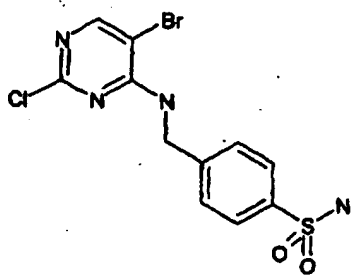


The title compound was made in a manner similar to Example 1D and deprotected similarly to Example 4C to give the desired material as its TFA salt in a 15% yield (tan solid). $C_{25}H_{25}BrN_6$. MS 489.0/491.1 (MH+); $^1$H NMR ($d_6$-DMSO) δ11.37 (s, 1 H), 8.91 (s, 1 H), 8.11 (s, 1 H), 7.94 (s, 1 H), 7.57 (s, 1 H), 7.40 (d, *J = 8.8 Hz*, 1 H), 7.30 – 7.22 (m, 7 H), 6.12 (s, 1 H), 4.06 (bs, 1 H), 3.77 – 3.75 (bs, 2 H), 3.38-3.36 (bs, 2 H), 2.76-2.75 (bs, 2 H), 1.57 (d, *J = 6.8 Hz*, 3 H) ppm.

Example 8

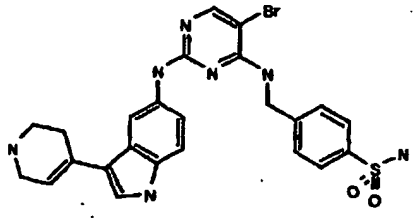
4-({5-Bromo-2-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-ylamino]-pyrimidin-4-ylamino}-methyl)-benzenesulfonamide

A. 4-[(5-Bromo-2-chloro-pyrimidin-4-ylamino)-methyl]-benzenesulfonamide



The title compound was made in a manner similar to Example 1A. It was isolated in a 30% yield as a white solid which fell out of solution upon work-up. $C_{11}H_{10}BrClN_4O_2S$. MS 375/377/378 (MH+). $^1$H NMR ($d_6$-DMSO) δ 8.26 (s, 1 H), 7.74 (d, *J = 8.6 Hz*, 2 H), 7.42 (d, *J = 8.6 Hz*, 2 H), 4.59 (s, 2 H) ppm.

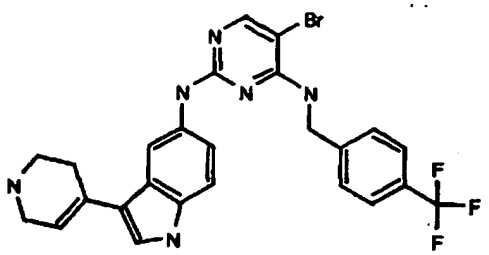
B. 4-({5-Bromo-2-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-ylamino]-pyrimidin-4-ylamino}-methyl)-benzenesulfonamide



The title compound was made in a manner similar to Example 1D and deprotected similarly to Example 4C. It was isolated as its free base after column chromatography (93:7:0.7 $CHCl_3$:$CH_3OH$:$NH_4OH$) as a brown solid in a 2% yield. $C_{24}H_{24}BrN_7O_2S$. MS: 554.1/556.0 (MH+). $^1$H NMR ($CD_3OD$) δ($CD_3OD$) δ 7.89 (s, 1 H), 7.68 (d, *J = 8.3 Hz*, 2 H), 7.31 (d, *J = 8.3 Hz*, 2 H), 7.26-7.22 (m, 2 H), 7.16-7.10 (m, 2H), 6.69 (d, *J = 8.7 Hz*, 1 H), 6.16 (bs, 1 H), 4.61 (bs, 2 H), 3.59-3.57 (bs, 2 H), 3.30 – 3.21 (bs, 2 H), 2.55 – 2.53 (bs, 2 H) ppm..

Example 9

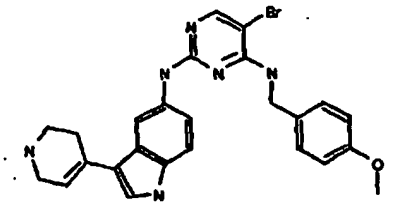
5-Bromo-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-$N^4$-(4-trifluoromethyl-benzyl)-pyrimidine-2,4-diamine



To a stirred solution of 5-bromo-2,4-dichloropyrimidine (0.222 g, 0.98 mmol) in THF (3 mL) under nitrogen was added triethylamine (0.42 mL, 3 mmol) followed by dropwise addition of p-trifluoromethylbenzyl amine (0.175 g,1 mmol). After three hours the THF was removed under reduced pressure. To the resulting residue was added dioxane (1 mL) followed by 4-(5-Amino-1H-indol-3-yl)-3,6-dihydro-2H-pyridine-1-carboxylic acid tert-butyl ester (0.345 g 1.1 mmol). The mixture was stirred under nitrogen and then heated to 110° C for sixteen hours. The reaction was cooled and was then dissolved in a solution of 5% methanol-dichloromethane and extracted with 1 N NaOH. The organic and aqueous layers were separated and the aqueous layer was further extracted with additional 5% methanol-dichloromethane. The organic layers were combined, washed with brine, dried over magnesium sulfate, filtered and evaporated under reduced pressure. The resulting residue was purified by silica gel chromotography (30% ethyl acetate in hexanes) to give 4-{5-[5-Bromo-4-(4-trifluoromethyl-benzylamino)-pyrimidin-2-ylamino]-1H-indol-3-yl}-3,6-dihydro-2H-pyridine-1-carboxylic acid tert-butyl ester (150 mg, 23%): (MS: 642.9/644.73 MH+). This material was then taken directly to the next reaction. To a stirred solution of 4-{5-[5-Bromo-4-(4-trifluoromethyl-benzylamino)-pyrimidin-2-ylamino]-1H-indol-3-yl}-3,6-dihydro-2H-pyridine-1-carboxylic acid tert-butyl ester (0.15 g) in dichloromethane (2 mL) at 0° C under nitrogen was added trifluoroacetic acid (4 mL). The cooling bath was removed and the reaction mixture was stirred for four hours. The reaction was concentrated under reduced pressure. To the resulting residue was added ethyl acetate (2 mL) followed by concentrating to an oily residue. The ethyl acetate concentration sequence was repeated three times. The resulting residue was suspended in ethyl acetate follow by addition of diethyl ether to precipitate 5-Bromo-N2-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-$N^4$-(4-trifluoromethyl-benzyl)-pyrimidine-2,4-diamine trfluoroacetate salt (0.129 g, 86%) as a white solid: $C_{25}H_{22}BrF_3N_6$. MS: 542.9/544.7 (MH+). $^1$H NMR ($D_6$-DMSO) δ 11.31 (s, 1 H), 8.82 (s, 2 H), 8.08 (s, 1 H), 7.88 (s, 1 H), 7.53 (s, 3 H), 7.36 (s, 2 H), 7.28 (d, *J = 8.3 Hz*, 1 H), 7.16 (d, *J = 8.3 Hz*, 1 H), , 6.05 (bs, 1 H), 4.58 (s, 2 H), 3.75-3.65 (bs, 2 H), 3.35-3.25 (bs, 2 H), 2.70-2.60 (bs, 2 H) ppm

Example 10

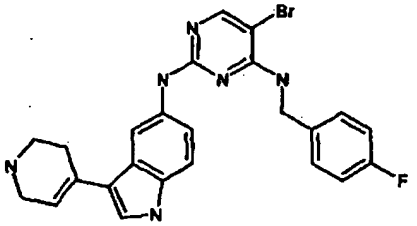
5-Bromo-$N^4$-(4-methoxy-benzyl)-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine



The title compound was synthesized according to the procedure of Example 9. It was isolated in a 21% yield as a white solid TFA salt. $C_{25}H_{25}BrN_6O$. MS: 505.0/506.8 (MH+); $^1H$ NMR ($D_6$-DMSO) δ 11.33 (s, 1 H), 8.84 (s, 2 H), 8.06 (s, 1 H), 7.95 (s, 1 H), 7.53 (s, 1 H), 7.35 (d, *J* = 7.9 Hz, 1 H), 7.23 (d, *J* = 7.9 Hz, 1 H), 7.10 (s, 2 H), 6.74 (s, 1 H), 6.73 (s, 1 H), 6.06 (s, 1 H), 4.26 (s, 2 H), 3.69 (s, 2 H), 3.66 (s, 3 H), 3.30 (s, 2 H), 2.68 (s, 2 H) ppm.

Example 11

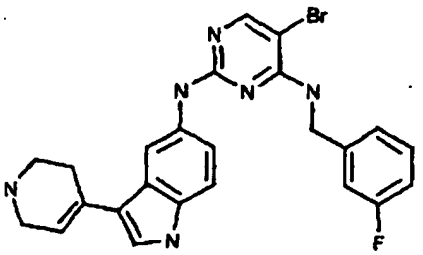
5-Bromo-$N^4$-(4-fluoro-benzyl)-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine



The title compound was synthesized according to the procedure of Example 9. It was isolated in a 12% overall yield as an off-white TFA salt. $C_{24}H_{22}BrFN_6$. MS: 492.9/494.9 (MH+); $^1H$ NMR ($D_6$-DMSO) δ 11.26 (s, 1 H), 8.78 (s, 2 H), 8.03 (s, 1 H), 7.95 (s, 1 H), 7.51 (s, 1 H), 7.31-7.23 (m, 3 H), 7.02 (s, 2 H), 6.05 (s, 1 H), 4.50 (s, 2 H), 3.70 (s, 2 H), 3.29 (s, 2 H), 2.68 (s, 2 H) ppm.

Example 12

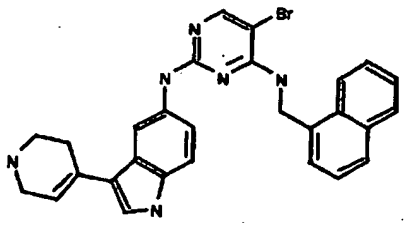
5-Bromo-$N^4$-(3-fluoro-benzyl)-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine



The title compound was synthesized in a manner similar to Example 9 in a 20% yield. It was isolated as an off-white solid TFA salt. $C_{24}H_{22}BrFN_6$. MS: 492.9/494.9 (MH+); $^1H$ NMR ($D_6$-DMSO) δ 11.33 (s, 1 H), 8.66 (s, 2 h), 8.40-8.20 (bs, 1 H), 8.11 (s, 1 H), 7.98 (s, 1 H), 7.57 (s, 1 H), 7.33-7.30 (m, 3 H), 7.10-7.07 (m, 3 H), 6.11 (s, 1 H), 4.60 (d, *J = 5.6 Hz*, 2 H), 3.77 (s, 2 H), 3.37 (s, 2 H), 2.73 (s, 2 H) ppm.

Example 13

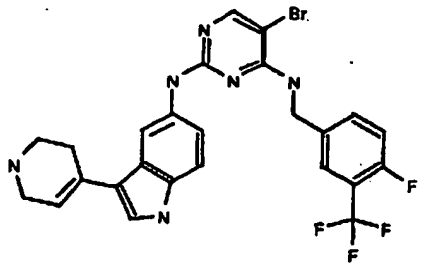
5-Bromo-$N^4$-naphthalen-1-ylmethyl-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine



The title compound was made in a manner described in Example 9 in a 16% yield. The isolated TFA salt was characterized as an off-white solid. $C_{28}H_{25}BrN_6$. MS: 525.1/527.1 (MH+); $^1H$ NMR ($D_6$-DMSO) δ 11.21 (s, 1 H), 8.76 (s, 2 H), 8.15 (d, *J = 9.2 Hz*, 1 H), 8.06 (s, 1 H), 7.93 (d, *J = 8.0 Hz*, 1 H), 7.89 (s, 1 H), 7.79 (d, *J = 7.8 Hz*, 1 H), 7.54-7.46 (m, 3 H), 7.34 (s, 1 H), 7.28 (s, 1 H), 7.14 (d, *J = 8.4 Hz*, 1 H), 6.98 (bs, 1 H), 6.02 (s, 1 H), 5.04 (s, 2 H), 3.67 (s, 2 H), 3.28 (s, 2 H), 2.65 (s, 2 H) ppm.

Example 14

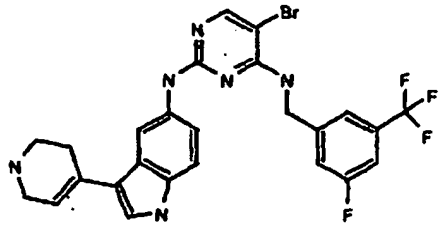
5-Bromo-$N^4$-(4-fluoro-3-trifluoromethyl-benzyl)-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine



The title compound was made in a manner described in Example 9 in a 12% overall yield. The isolated TFA salt was characterized as an off-white solid. $C_{25}H_{21}BrF_4N_6$. MS: 560.8/562.4 (MH+); $^1H$ NMR ($D_6$-DMSO) δ11.31 (s, 1 H), 8.87 (s, 2 H), 8.24 (bs. 1 H), 8.11 (s, 1 H), 8.01 (s, 1 H), 7.72 (s, 1 H), 7.56 (s, 2 H), 7.36-7.29 (m, 3 H), 6.18 (s, 1 H), 4.62 (d, *J = 5.6 Hz*, 2 H), 3.79 (s, 2 H), 3.39 (s, 2 H), 2.74 (s, 2 H) ppm.

Example 15

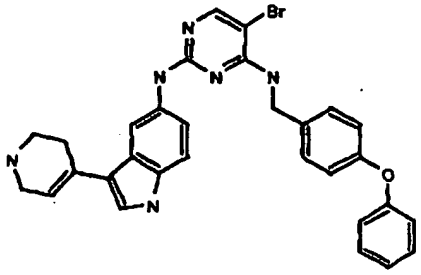
5-Bromo-$N^4$-(3-fluoro-5-trifluoromethyl-benzyl)-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine



The title compound was synthesized in a manner described in Example 9 in a 16% overall yield. It was characterized as an off-white solid as its TFA salt. $C_{25}H_{21}BrF_4N_6$. MS: 561.4/563.2 (MH+), $^1$H NMR ($D_6$-DMSO) δ 11.26 (s, 1 H), 8.82 (s, 2 H), 8.21 (bs, 1 H), 8.07 (s, 1 H), 7.94 (s, 1 H), 7.46-7.35 (m, 3 H), 7.24 (s, 1 H), 7.20 (s, 2 H), 6.06 (s, 1 H), 4.61 (d, *J* = *5.4 Hz*, 2 H), 3.74 (s, 2 H), 3.30 (s, 2 H), 2.68 (s, 2 H) ppm.

Example 16

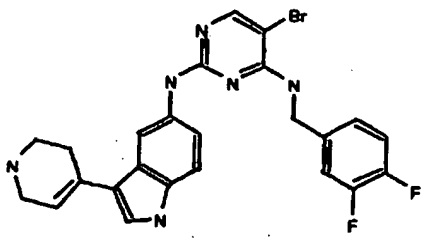
5-Bromo-$N^4$-(4-phenoxy-benzyl)-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine



The title compound was synthesized in a 9% overall yield in a manner described in Example 9. It was characterized as an off-white solid isolated as its TFA salt. $C_{30}H_{27}BrN_6O$. 567.0/568.6 (MH+); $^1$H NMR ($CD_3OD$) δ 7.89 (s, 1 H), 7.84 (s, 1 H), 7.48 (s, 1 H), 7.47 (d, *J* = *7.5 Hz*, 1 H), 7.31 (dd, *J* = *7.5, .3 Hz*, 2 H), 7.17 (d, *J* = *8.7 Hz*, 1 H), 7.15 (bs, 2 H), 7.08 (t, *J* = *7.5 Hz*, 1 H), 6.90 (d, *J* = *8.3 Hz*, 2 H), 6.79 (s, 2 H), 6.15 (s, 1 H), 4.57 (s, 2 H), 3.80 (s, 2 H), 3.42 (s, 2 H), 2.82 (s, 2 H) ppm.

Example 17

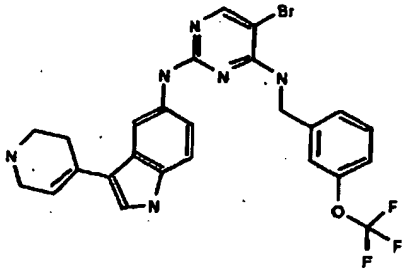
5-Bromo-$N^4$-(3,4-difluoro-benzyl)-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine



The title compound was synthesized in a 19% overall yield in a manner described in Example 9. It was characterized as an off-white solid isolated as its TFA salt. $C_{24}H_{21}BrF_2N_6$: 510.9/513 .0 (MH+); $^1$H NMR ($D_6$-DMSO) δ 11.26 (s, 1 H), 8.87 (bs, 2 H), 8.09 (s, 2 H), 8.00 (s, 1 H), 7.56 (s, 1H), 7.33 (m, 3 H), 7.10 (s, 1 H), 6.11 (s, 1 H), 4.54 (s, 2 H), 3.78 (s, 2 H), 3.35 (s, 2 H), 2.74 (s, 2 H) ppm.

Example 18

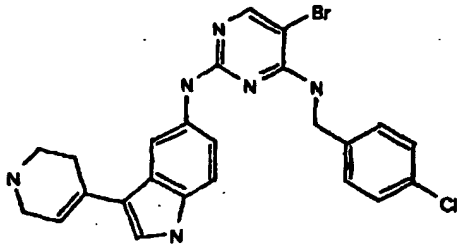
5-Bromo-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-$N^4$-(3-trifluoromethoxy-benzyl)-pyrimidine-2,4-diamine



The title compound was synthesized in a 8% ovrall yield in a manner described in Example 9. It was characterized as an off-white solid isolated as its TFA salt. $C_{25}H_{22}BrF_3N_6O$. 559.0/561.0 (MH+); $^1$H NMR ($D_6$-DMSO) δ 11.28 (s, 1 H), 8.81 (bs, 2 H), 8.08 (s, 1 H), 8.01 (s, 1 H), 7.55 (s, 1 H), 7.50 (bs, 1 H), 7.40-7.21 (m, 6 H), 6.10 (s, 1 H), 4.63 (s, 2 H), 3.77 (s, 2 H), 3.37 (s, 2 H), 2.73 (s, 2 H) ppm.

Example 19

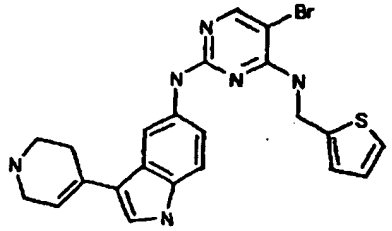
5-Bromo-$N^4$-(4-chloro-benzyl)-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine



The title compound was synthesized in a 20% overall yield in a manner described in Example 9 from 4-chlorobenzyl amine. It was characterized as an off-white solid isolated as its TFA salt. $C_{24}H_{22}BrClN_6$. MS: 508.9/510.9/513.0 (MH+); $^1$H NMR ($D_6$-DMSO) δ 11.27 (s, 1 H), 8.85 (bs, 2 H), 8.09 (s, 1 H), 7.98 (s, 1 H), 7.56 (s, 1 H), 7.32-7.29 (*m*, 6 H), 6.10 (s, 1 H), 4.55 (s, 2 H), 3.77 (s, 2 H), 3.36 (s, 2 H), 2.74 (s, 2 H) ppm.

Example 20

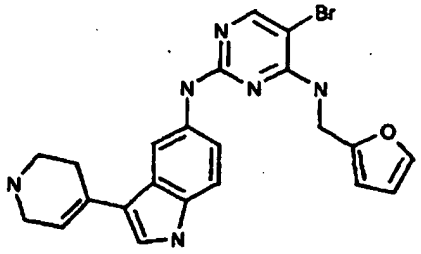
5-Bromo-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-$N^4$-thiophen-2-ylmethyl-pyrimidine-2,4-diamine



The title compound was synthesized in a 12% overall yield in a manner described in Example 9 from 2-methylaminothiophene. It was characterized as an off-white solid isolated as its TFA salt. $C_{22}H_{21}BrN_6S$. MS: 481.0/483.0 (MH+); $^1$H NMR ($D_6$-DMSO) δ 11.24 (s, 1 H), 8.77 (s, 2 H), 8.04 (s, 2 H), 7.49 (s, 1 H), 7.32 (s, 3 H), 6.87 (m, 2 H), 6.05 (s, 1 H), 4.71 (s, 2 H), 3.69 (s, 2 H), 3.29 (s, 2 H), 2.67 (s, 2 H) ppm.

Example 21

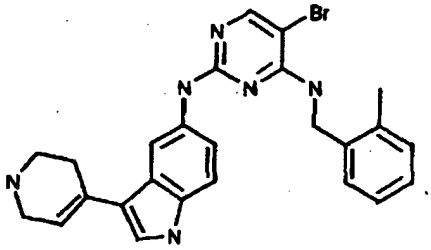
5-Bromo-N4-furan-2-ylmethyl-N2-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine



The title compound was made in a manner similar to Example 9. It was isolated in a 1% yield as an off-white solid characterized as its free base. $C_{22}H_{21}BrN_6O$. MS: 465.1/467.1 (MH+)

Example 22

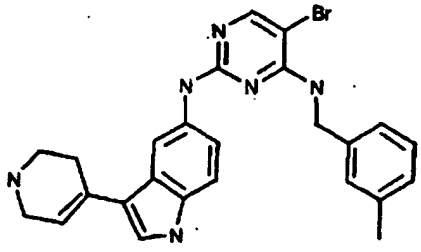
5-Bromo-$N^4$-(2-methyl-benzyl)-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine



$C_{25}H_{25}BrN_6$.

Example 23

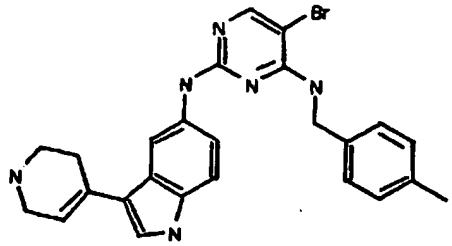
5-Bromo-$N^4$-(3-methyl-benzyl)-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine



$C_{25}H_{25}BrN_6$.

Example 24

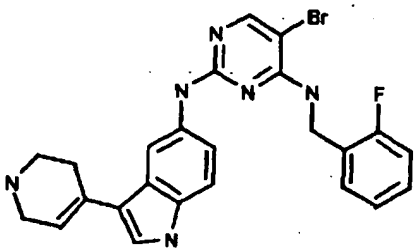
5-Bromo-$N^4$-(4-methyl-benzyl)-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine



$C_{25}H_{25}BrN_6$.

Example 25

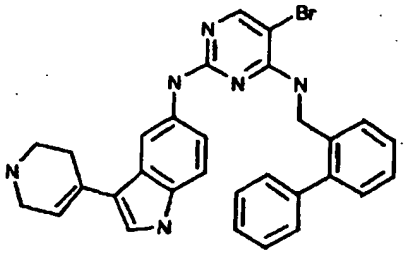
5-Bromo-$N^4$-(2-fluoro-benzyl)-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine



$C_{24}H_{22}BrFN_6$.

Example 26

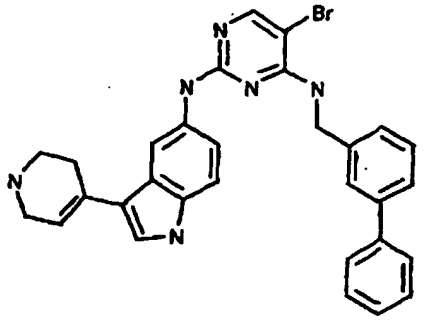
$N^4$-Biphenyl-2-ylmethyl-5-bromo-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine



$C_{30}H_{27}BrN_6$.

Example 27

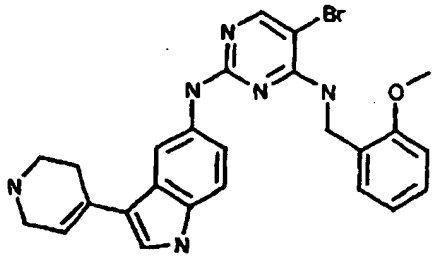
$N^4$-Biphenyl-3-ylmethyl-5-bromo-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine



$C_{30}H_{27}BrN_6$.

Example 28

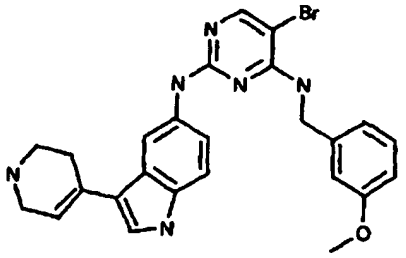
5-Bromo-$N^4$-(2-methoxy-benzyl)-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine



$C_{25}H_{25}BrN_6O$.

Example 29

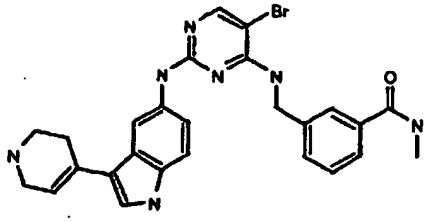
5-Bromo-$N^4$-(3-methoxy-benzyl)-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine



$C_{25}H_{25}BrN_6O$.

Example 30

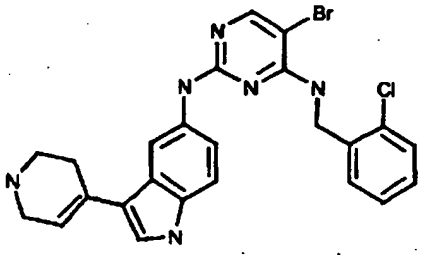
3-({5-Bromo-2-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-ylamino]-pyrimidin-4-ylamino}-methyl)-N-methyl-benzamide



$C_{28}H_{28}BrN_7O$.

Example 31

5-Bromo-$N^4$-(2-chloro-benzyl)-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine

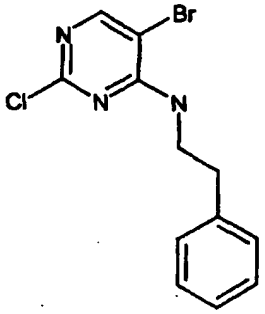


$C_{24}H_{22}BrClN_6$.

Example 32

5-Bromo-$N^4$-phenethyl-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine

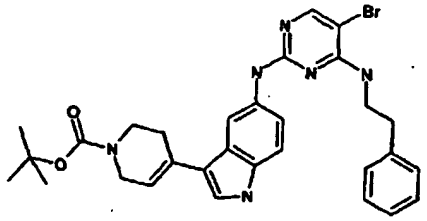
A. (5-Bromo-2-chloro-pyrimidin-4-yl)-phenethyl-amine



A 5.00 g (22.0 mmol) sample of 5-bromo-2,4-dichloropyrimidine was taken into 40.0 mL tetrahydrofuran with 7.80 mL (44.8 mmol) diisopropylethylamine. 3.53 g (22.4 mmol) phenethyl amine was added drop-wise with a white precipitate noted upon addition. After addition mLetion, the reaction mixture was allowed to stir at ambient temperature under

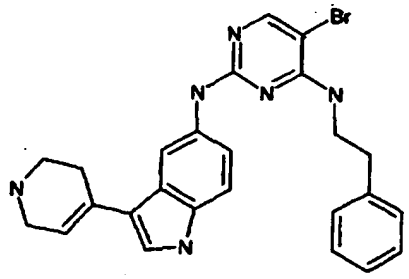
nitrogen for three hours. The volatiles were removed under reduced pressure, and the resulting residue was partitioned between 1 N sodium hydroxide and ethyl acetate. Aqueous work-up afforded the title compound as 5.93 g (19.0 mmol, 95%) of a pale yellow, oily solid. $C_{12}H_{11}BrClN_5$: GC/MS: ret. Time: 4.77 min.: m/z 311/313/315, 220/222/224, 104; $^1$H NMR ($CDCl_3$) δ 8.09 (s, 1 H), 7.34 - 7.30 (m, 2 H), 7.28 - 7.18 (m, 3 H), 5.53 (bs, 1 H), 3.75 (t, *J* = *6.4 Hz*, 2 H), 2.92 (t, *J* = *6.4 Hz*, 2 H) ppm.

B. 4-[5-(5-Bromo-4-phenethylamino-pyrimidin-2-ylamino)-1H-indol-3-yl]-3,6-dihydro-2H-pyridine-1-carboxylic acid tert-butyl ester



The title compound was made in a 35% yield in a manner similar to Example 1D using (5-bromo-2-chloro-pyrimidin-4-yl)-phenethyl-amine. $C_{30}H_{33}BrN_6O_2$: MS 589.1/591.1 (MH+); $^1$H NMR ($D_6$-DMSO): δ 11.00 (s, 1 H), 8.92 (s, 1 H), 7.94 (s, 1 H), 7.40 (d, *J* = *8.4 Hz*, 1 H), 7.34 (s, 1 H), 7.22 (d, *J* = *8.4 Hz*, 1 H), 7.18 - 7.07 (m, 6 H), 6.90 (m, 1 H), 6.02 (s, 1 H), 3.98 (m, 2 H), 3.56 (m, 2 H), 3.45 (m, 2 H), 2.76 (t, *J* = *7.6 Hz*, 2 H), 2.42 (m, 2 H), 1.38 (s, 9 H) ppm.

C. 5-Bromo-N4-phenethyl-N2-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine



832 mg (1.70 mmol) 4-[5-(5-Bromo-4-phenethylamino-pyrimidin-2-ylamino)-1H-indol-3-yl]-3,6-dihydro-2H-pyridine-1-carboxylic acid tert-butyl ester was taken into 2.00 mL dichloromethane and cooled to 0° C. 4.00 mL trifluoroacetic acid was slowly added. The red reaction mixture was allowed to stir under nitrogen and slowly warm to ambient temperature over three hours. The volatiles were removed under reduced pressure. Ethyl acetate was added and evaporated an additional three times until a nearly clear yellow oil remained. Ethyl acetate was added (app. 1 mL) and stirred. Diethyl ether was added until a white precipitate was noted. Filtration of this precipitate afforded 716 mg of the title compound isolated as its Trifluoroacetate salt. $C_{25}H_{25}BrN_6$: MS: 489.1/491.1 (MH+); $^1$H NMR ($D_6$-DMSO): δ 11.45 (s,

1 H), 10.32 (s, 1 H), 8.92 (s, 1 H), 8.31 (s, 1 H), 8.16 (s, 1 H), 7.91 (s, 1 H), 7.57 (s, 1 H), 7.40 (d, *J* = 8.3 Hz, 1 H), 7.27 (d, *J* = 8.3 Hz, 1 H), 7.11 - 6.90 (m, 5 H), 6.19 (bs, 1 H), 3.68 (m, 2 H), 3.46 (m, 2 H), 3.24 (m, 2 H), 2.71 - 2.66 (m, 4 H) ppm.

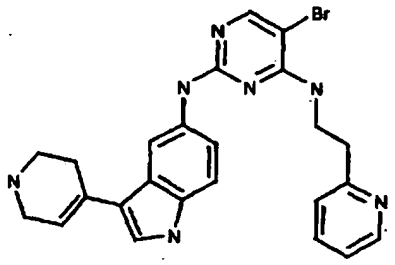
Example 33

5-Bromo-$N^4$-(2-pyridin-2-yl-ethyl)-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine

A. (5-Bromo-2-chloro-pyrimidin-4-yl)-(2-pyridin-2-yl-ethyl)-amine

The title compound was made in a manner similar to Example 32A. It was isolated in an 83% yield as a tan solid. $C_{11}H_{10}BrClN_4$. MS 313.0/315.0/317.0 (MH+); $^1$H NMR ($D_6$-DMSO) δ 8.53 (d, *J* = 4.9 Hz, 1 H), 8.26 (s, 1 H), 7.92 (t, *J* = 5.5 Hz, 1 H), 7.73 (t, *J* = 7.6 Hz, 1 H), 7.30-7.23 (m, 2 H), 3.78-3.62 (m, 2 H), 3.07-3.02 (m, 2 H) ppm.

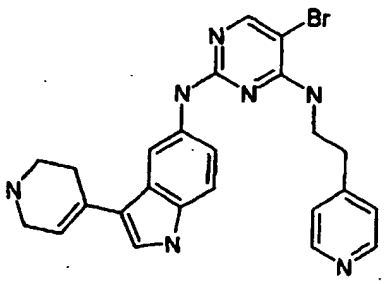
B. 5-Bromo-N4-(2-pyridin-2-yl-ethyl)-N2-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine



The title compound was synthesized in a manner similar to Example 32B and deprotected similarly to Example 21C. It was made in a 40% yield and isolated as a white solid, TFA salt. $C_{24}H_{24}BrN_7$. MS: 490.0/491.8 (MH+); $^1$H NMR ($D_6$-DMSO) δ 11.41 (s, 1 H), 8.89 (s, 2H), 8.59 (s, 1 H), 8.29-8.00 (m, 2H), 7.91 (s, 2 H), 7.56-7.50 (m, 2H), 7.38 (d, *J* = 8.3 Hz, 1 H), 7.35-7.20 (m, 2 H), 6.07 (bs, 1 H), 3.98-3.72 (bs, 4 H), 3.37-3.30 (bs, 2 H), 3.10-3.00 (bs, 2 H), 2.67-2.46 (bs, 2 H) ppm.

Example 34

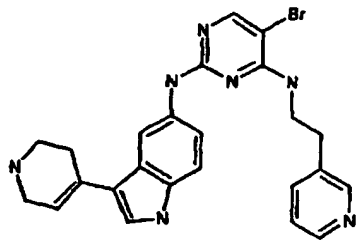
5-Bromo-$N^4$-(2-pyridin-4-yl-ethyl)-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine



The title compound was made in a 30% yield in the same manner as Example 9 using 4-(2-ethylamino)pyridine. It was noted to be a white solid, isolated as its TFA salt. $C_{24}H_{24}BrN_7$. MS: 490.0/492.0 (MH+); $^1$H NMR ($D_6$-DMSO) δ11.37 (s, 1 H),8.85 (s, 1H), 8.50 (s, 2 H), 8.10 (s, 1 H), 7.94 (s, 1 H), 7.54 (s, 1H), 7.37 (d, *J = 8.7 Hz*, 1 H), 7.35 (bs, 1 H), 7.26 (d, *J = 9.1 Hz*, 1 H), 6.06 (bs, 1 H), 3.75-3.65 (bs, 2 H), 3.60-3.50 (bs, 2 H), 3.35-3.25 (bs, 2 H), 3.00-2.90 (bs, 2 H), 2.70-2.60 (bs, 2H) ppm.

Example 35

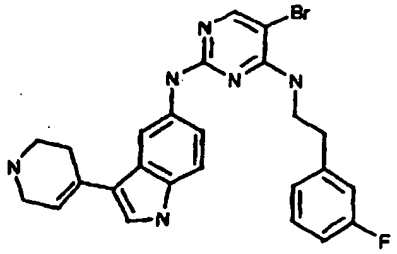
5-Bromo-$N^4$-(2-pyridin-3-yl-ethyl)-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine



The title compound was made in a 23% overall yield starting from 3(2-ethylamino)pyridine, following the procedure of Example 9. The compound was noted to be an off-white solid isolated as its TFA salt. $C_{24}H_{24}BrN_7$. MS: 490.2/492.2 (MH+); $^1$NMR ($D_6$-DMSO) δ 11.37 (s, 1 H), 8.82 (s, 2H), 8.53 (s, 1 H), 8.49 (s, 1 H), 8.09 (s, 1H), 8.00 (bs, 1H), 7.97 (s, 1 H), 7.66 (bs, 1 H), 7.54 (s, 1 H), 7.39 (bs, 1 H), 7.37 (d, *J = 8.8* Hz, 1 H), 7.26 (d, *J = 8.3* Hz, 1 H), 6.07 (bs, 1 H), 3.70 (s, 2 H), 3.55(s, 2 H), 3.28(s, 2 H), 2.88 (s, 2 H), 2.70-2.60 (bs, 2 H) ppm..

Example 38

5-Bromo-$N^4$-[2-(3-fluoro-phenyl)-ethyl]-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine

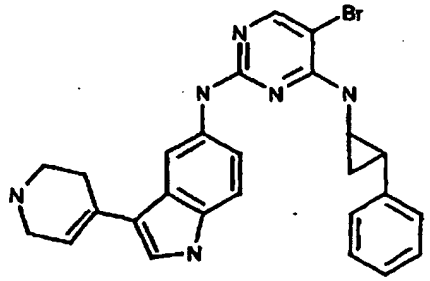


The title compound was isolated in a 4% yield as a white solid according to the procedure of Example 9. It was isolated as its free base after purifying over silica gel (93:7:0.7 $CHCl_3$:$CH_3OH$:$NH_4OH$). $C_{25}H_{24}BrFN_8$. MS: 507.0/508.8 (MH+); $^{19}$F NMR ($D_6$-DMSO) δ -114.0 ppm. $^1$H NMR ($D_6$-DMSO) δ 10.90 (s, 1 H), 8.92 (s, 1 H), 8.08 (s, 1 H), 7.93 (s, 1 H),

7.41 (dd, *J = 1.6, 8.7 Hz*, 1 H), 7.32 (s, 1 H), 7.27 (s, 1 H), 7.21-7.19 (m, 2 H), 6.99-6.88 (m, 4 H), 6.08 (s, 1 H), 3.59-3.53 (m, 2 H), 3.31 (s, 2 H), 2.85-2.82 (m, 4 H), 2.32 (s, 2 H) ppm.

Example 37

5-Bromo-$N^4$-(2-phenyl-cyclopropyl)-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine



The title compound was synthesized in a 13% overall yield in a manner described in Example 1. $C_{26}H_{25}BrN_6$. 501.0/503.0 (MH+); $^1$H NMR ($D_6$-DMSO) δ 11.28 (s, 1 H), 8.90 (bs, 2 H), 8.11 (s, 1 H), 7.90 (bs, 1 H), 7.86 (s, 1 H), 7.55 (s, 1 H), 7.43 (d, *J = 8.1 Hz*, 1 H), 7.21-7.09 (m, 6 H), 6.08 (s, 1 H), 3.77 (s, 2 H), 3.34 (m, 3 H), 2.73 (s, 2 H), 2.25 (m, 1 H), 1.58 (m, 1 H), 1.20 (m, 1 H) ppm.

Example 37A

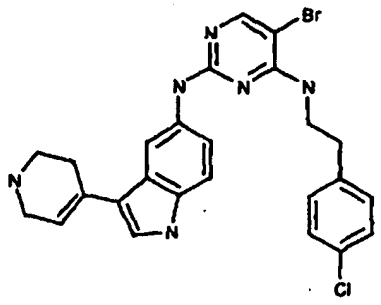
5-Bromo-$N^4$-(2-phenyl-cyclopropyl)-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine (homo-chiral)

Example 37B

5-Bromo-$N^4$-(2-phenyl-cyclopropyl)-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine (homo-chiral)

Example 38

5-Bromo-$N^4$-[2-(4-chloro-phenyl)-ethyl]-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine

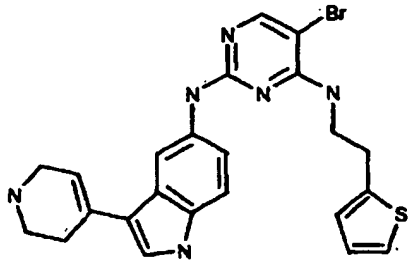


The title compound was isolated in a 10% overall yield in a manner described by Example 9 from 4-chlorophenethyl amine. It was characterized as an off-white solid isolated as its TFA salt. $C_{25}H_{24}BrClN_6$. MS: 522.9/524.9/527.0 (MH+); $^1$H NMR ($D_6$-DMSO) δ 11.37 (s,

1 H), 8.79 (s, 2 H), 8.07 (s, 1 H), 7.93 (s, 1 H), 7.56 (s, 1 H), 7.37 (d, *J* = 8.8 *Hz*, 1 H), 7.30 (s, 1 H), 7.13 (bs, 2 H), 6.97 (s, 2 H), 6.06 (s, 1 H), 3.69 (s, 2 H), 3.34 (s, 2 H), 3.26 (s, 2 H), 2.67 (m, 4 H) ppm.

Example 39

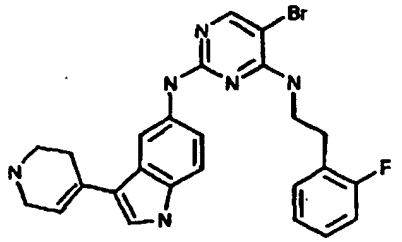
5-Bromo-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-$N^4$-(2-thiophen-2-yl-ethyl)-pyrimidine-2,4-diamine



The title compound was isolated in 13% overall yield in a manner described by Example 9 from 2-ethylaminothiophene. It was characterized as an off-white solid isolated as its TFA salt. $C_{23}H_{23}BrN_6S$. MS: 495.1/497.1 (MH+); $^1$H NMR ($D_6$-DMSO) δ 11.38 (s, 1 H), 8.86 (s, 2 H), 8.11 (s, 1 H), 8.00 (s, 1 H), 7.57 (s, 1 H), 7.39 (s, 2 H), 7.35 (d, *J* = 5.3 *Hz*, 1 H), 6.94 (m, 1 H), 6.78 (s, 1 H), 6.11 (s, 1 H), 3.75 (s, 2 H), 3.62 (s, 2 H), 3.34 (s, 2 H), 3.09 (s, 2 H), 2.72 (s, 2 H) ppm.

Example 40

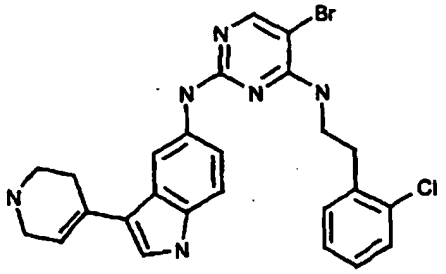
5-Bromo-$N^4$-[2-(2-fluoro-phenyl)-ethyl]-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine



The title compound was made in a 12% yield in a manner described in Example 9. It was characterized as an off-white solid isolated as its HCl salt. $C_{25}H_{24}BrFN_6$. MS: 507.0/508.9 (MH+); $^1$HNMR ($D_6$-DMSO) δ 11.43 (s, 1 H), 10.37 (s, 1 H), 9.20 (s, 2 H), 8.53 (bs, 1 H), 8.20 (bs, 1 H), 7.90 (s, 1 H), 7.57 (s, 1 H), 7.41 (s, 1 H), 7.18-7.06 (m, 3 H), 6.89 (bs, 1 H), 6.06 (s, 1 H), 3.66 (s, 2 H), 3.46 (s, 2 H), 3.23 (s, 2 H), 2.80 (s, 2 H), 2.67 (s, 2 H) ppm.

Example 41

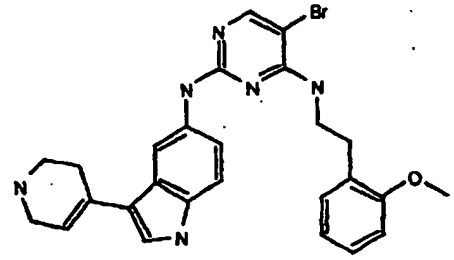
5-Bromo-$N^4$-[2-(2-chloro-phenyl)-ethyl]-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine



The title compound was made in a 20% yield in a manner described in Example 9. It was characterized as an off-white solid and isolated as its HCl salt. $C_{25}H_{24}BrClN_6$. MS: 523.1/525.1/527.1 (MH+); $^1$HNMR ($D_6$-DMSO) δ 11.45 (s, 1 H), 10.37 (s, 1 H), 9.17 (bs, 2 H), 8.54 (s, 1 H), 8.28 (s, 1 H), 7.87 (s, 1 H), 7.57 (s, 1 H), 7.42 (d, *J* = *8.7 Hz*, 1 H), 7.33 (d, *J* = *7.5 Hz*, 1 H), 7.22-7.17 (m, 2 H), 6.98 (bs, 1 H), 6.06 (s, 1 H), 3.66 (s, 2 H), 3.52 (s, 2 H), 3.22 (s, 2 H), 2.90 (s, 2 H), 2.67 (s, 2 H) ppm.

Example 42

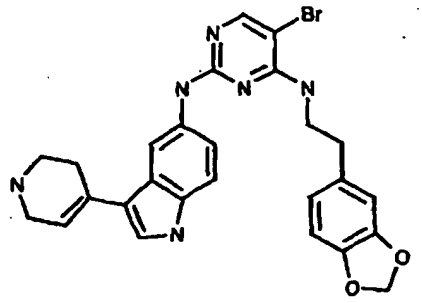
5-Bromo-$N^4$-[2-(2-methoxy-phenyl)-ethyl]-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine



The title compound was made in a 6% yield in a manner described in Example 9. It was characterized as an off-white solid and isolated as its HCl salt. $C_{26}H_{27}BrN_6O$. MS: 519.0/520.9 (MH+); $^1$HNMR ($D_6$-DMSO) δ 11.47 (s, 1 H), 10.46 (s, 1 H), 9.28 (bs, 2 H), 8.56 (s, 1 H), 7.90 (s, 1 H), 7.57 (s, 1 H), 7.41 (d, *J* = *8.8 Hz*, 1 H), 7.20 (s, 1 H), 7.17 (s, 1 H), 6.85 (d, *J* = *7.9 Hz*, 1 H), 6.65 (bs, 2 H), 6.05 (s, 1 H), 3.76 (s, 3 H), 3.65 (s, 2 H), 3.53 (s, 2 H), 3.20 (s, 2 H), 2.75 (s, 2 H), 2.67 (s, 2 H) ppm.

Example 43

$N^4$-(2-Benzo[1,3]dioxol-5-yl-ethyl)-5-bromo-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine

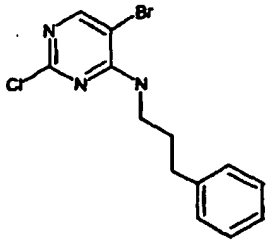


The title compound was made in a 4% yield in a manner described in Example 9. It was characterized as an off-white solid isolated as its HCl salt. $C_{26}H_{25}BrN_6O_2$. MS: 533.6/535.6 (MH+); $^1$HNMR ($D_6$-DMSO) δ 11.47 (s, 1 H), 10.43 (s, 1 H), 9.29 (bs, 2 H), 8.53 (s, 1 H), 8.34 (s, 1 H), 7.88 (s, 1 H), 7.67 (s, 1 H), 7.42 (s, 1 H), 7.22 (s, 1 H), 6.60 (m, 2 H), 6.05 (s, 1 H), 3.63 (s, 2 H), 3.52 (s, 2 H), 3.45 (s, 2 H), 2.69 (m, 4 H) ppm.

Example 44

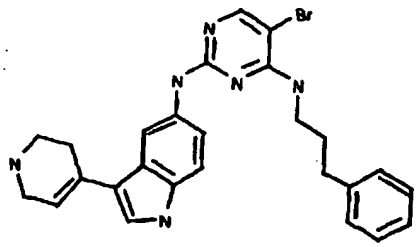
5-Bromo-$N^4$-(3-phenyl-propyl)-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine

A. (5-Bromo-2-chloro-pyrimidin-4-yl)-(3-phenyl-propyl)-amine



The title compound was made in a manner similar to Example 1A except performing the reaction at ambient temperature. It was isolated as a yellow oil which solidified upon standing in a 84% yield. MS: 324/326/328 (MH+); $^1$H NMR ($CDCl_3$) δ 8.30 (s, 1 H), 7.37-7.23 (m, 5 H), 5.52 (s, 1 H), 3.57 (tt, *J = 7.5, 7.3 Hz*, 2 H), 2.77 (t, *J = 7.5 Hz*, 2 H), 2.04 (t, *J = 7.3 Hz*, 2 H) ppm.

B. 5-Bromo-$N^4$-(3-phenyl-propyl)-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine

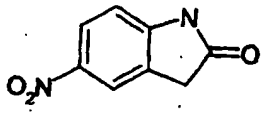


The title compound was isolated as its TFA salt following the procedure of Example 1D and deprotecting according Example 4C in a 34% yield as a white solid. $C_{25}H_{27}BrN_6$. MS: 503.2/505.1 (MH+); $^1$H NMR ($D_6$-DMSO) δ 11.32 (s, 1 H), 8.90 (s, 1 H), 8.05 (s, 1 H), 7.93 (s, 1 H), 7.53 (s, 1 H), 7.35 (s, 2H), 7.21-7.05 (m, 7 H), 6.07 (bs, 1 H), 3.80-3.70 (bs, 2 H), 3.37–3.31 (bs, 4 H), 2.70-2.60 (bs, 2 H), 2.47-2.46 (bs, 2 H), 2.00-1.90 (bs, 2 H).

Example 45

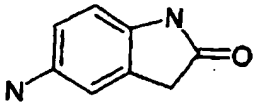
5-(5-Bromo-4-phenethylamino-pyrimidin-2-ylamino)-1,3-dihydro-indol-2-one

A. 5-Nitro-1,3-dihydro-indol-2-one



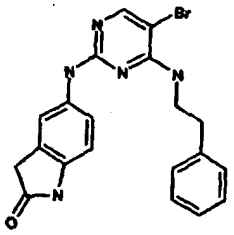
$C_8H_6N2O_3$: GC/MS ret. time: 4.12 min., m/z 178, 148, 104; $^1$H NMR ($D_6$-DMSO) d 10.50 (s, 1 H), 8.11 (d, *J = 8.7 Hz*, 1 H), 8.05 (s, 1 H), 6.94 (d, *J = 8.7 Hz*, 1 H), 3.59 (s, 2 H) ppm.

B. 5-Amino-1,3-dihydro-indol-2-one



To 250 mL acetic acid was added 7.00 g (39.3 mmol) 5-nitro-1,3-dihydro-indol-2-one and 418 mg (0.393 mmol) palladium on carbon. Exposed the reaction mixture to 40 psi $H_2$ on parr shaker for 1.5 hours. The reaction was filtered through diatameceous earth, and the acetic acid was removed under reduced pressure. Cooled the reaction mixture to 0° C and added 10.0 mL of a 94.5:5:0.5 $CHCl_3$:$CH_3OH$:$NH_4OH$ solution. The solution was loaded onto a silica gel column and purified via chromatography (97.8:2.0:0.2 $CHCl_3$:$CH_3OH$:$NH_4OH$) to give a white solid which was further crystallized using the eluent as the solvent to give 4.06 g (27.2 mmol, 69%) of the title compound as crystalline white needles. $C_8H_8N2O$:

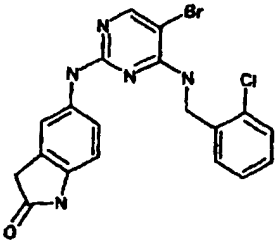
C. 5-[5-Bromo-4-phenethylamino-pyrimidin-2-ylamino)-1,3-dihydro-indol-2-one



153 mg (0.490 mmol) (5-Bromo-2-chloro-pyrimidin-4-yl)-phenethyl-amine was taken into 500 □L 1,4 dioxane with 140 □L (1.00 mmol) diisopropylethylamine and 80 mg (0.539 mmol) 5-amino-1,3-dihydro-indol-2-one. The reaction was allowed to heat to 110° C for sixteen hours. The resulting brown glass was taken into 92.3:7:0.7 $CHCl_3$:$CH_3OH$:$NH_4OH$ and washed with 1 N sodium hydroxide. The organic layer was dried over magnesium sulfate and evaporated directly onto silica gel. This adsorbed compound was purified via column chromatography (97.8:2:0.2 $CHCl_3$:$CH_3OH$:$NH_4OH$) over silica to isolate the major product. During evaporation of the major fractions, a white precipitate is noted. Filtration of this precipitate prior to mLete evaporation afforded the title compound in 6% yield as a white solid. $C_{20}H_{18}BrN_5O$: MS: 424.2/426.2 (MH+); $^1H$ NMR ($D_6$-DMSO) 10.20 (s, 1 H), 9.01 (s, 1 H), 7.93 (s, 1 H), 7.52 (s, 1 H), 7.44 (d, *J* = 8.4 Hz, 1 H), 7.28 - 7.16 (m, 5 H), 6.97 (m, 1 H), 6.65 (d, *J* = 8.3 Hz, 1 H), 3.56 (m, 2 H), 3.31 (s, 2 H), 2.82 (t, *J* = 7.9 Hz, 2 H) ppm.

Example 46

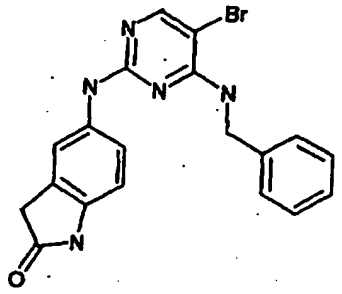
5-[5-Bromo-4-(2-chloro-benzylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one



$C_{19}H_{15}BrClN_5O$.

Example 47

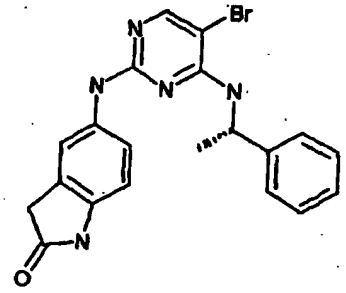
5-(4-Benzylamino-5-bromo-pyrimidin-2-ylamino)-1,3-dihydro-indol-2-one



$C_{19}H_{16}BrN_5O$

Example 48

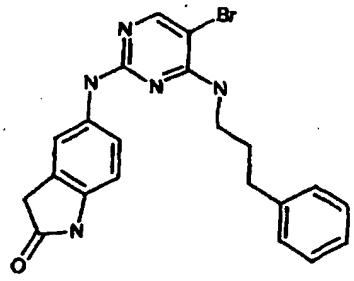
5-[5-Bromo-4-(1-phenyl-ethylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one



$C_{20}H_{18}BrN_5O$.

Example 49

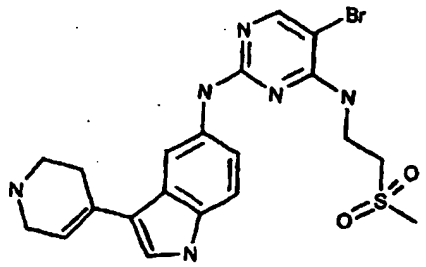
5-[5-Bromo-4-(3-phenyl-propylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one



$C_{21}H_{20}BrN_5O$.

Example 50

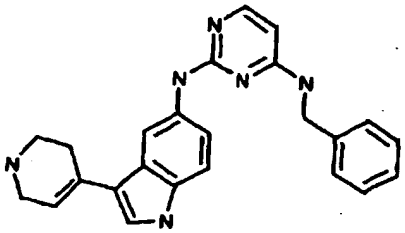
5-Bromo-$N^4$-(2-methanesulfonyl-ethyl)-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine



The title compound was made in a 13% yield in a manner described in Example 9. It was characterized as an off-white solid isolated as it TFA salt. $C_{20}H_{23}BrN_6O_2S$: MS: 491.1/493.1 (MH+); $^1$H NMR ($D_6$-DMSO) δ 11.28 (s, 1 H), 8.84 (s, 2 H), 8.09 (s, 1 H), 7.95 (s, 1 H), 7.83 (s, 1 H), 7.52 (s, 1 H), 7.38 (s, 1 H), 7.36 (s, 1 H), 6.07 (s, 1 H), 3.75 (m, 4 H), 3.34 (m, 4 H), 2.90 (s, 3 H), 2.69 (m, 2 H) ppm.

Example 51

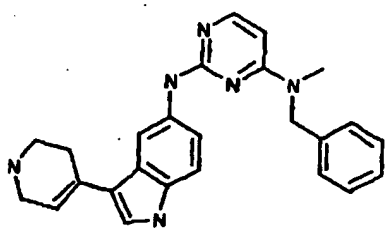
$N^4$-Benzyl-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine



250 mg (0.424 mmol) $N^4$-Benzyl-5-bromo-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine trifluoroacetate was suspended in 12.7 mL conc. $NH_4OH$. To this was added 0.636 g (9.73 mmol) zinc dust. The resulting slurry was heated to reflux for three hours. The gray mixture was filtered through diatomaceous earth. The filtrate was evaporated under reduced pressure to give the title compound in 39% yield isolated as a white solid. $C_{24}H_{24}N_6$. MS: 397.2 (MH+); $^1$H NMR ($CD_3OD$) δ 8.05 (s, 1 H), 7.66 (d, $J$ = 5.8 Hz, 1 H), 7.30-7.17 (m, 7 H), 6.15 (s, 1 H), 5.87 (d, $J$ = 5.8 Hz, 1 H), 4.55 (s, 2 H), 3.41 (s, 2 H), 3.05 (s, 2 H), 2.53 (s, 2 H) ppm.

Example 52

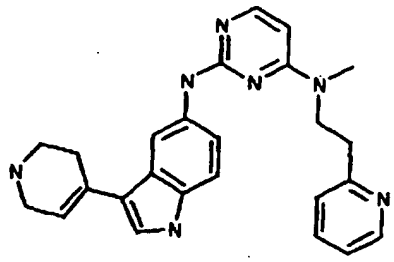
$N^4$-Benzyl-$N^4$-methyl-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine



The title compound was synthesized in a 4% overall yield in a manner similar to Example 9 using 2-4-dichloropyrimidine and N-methyl benzyl amine. It was characterized as an off-white solid isolated as its free base. $C_{25}H_{26}N_6$. MS: 411.2 (MH+); $^1$H NMR ($D_6$-DMSO) δ 10.85 (s, 1 H), 8.23 (s, 1 H), 7.88 (d, *J = 5.8 Hz*, 1 H), 7.35-7.15 (m, 9 H), 6.07 (s, 1 H), 6.04 (d, *J = 5.8 Hz*, 1 H), 4.78 (s, 2 H), 3.32 (s, 2 H), 3.13 (s, 2 H), 2.93 (m, 2 H), 2.47 (s, 3 H) ppm.

Example 53

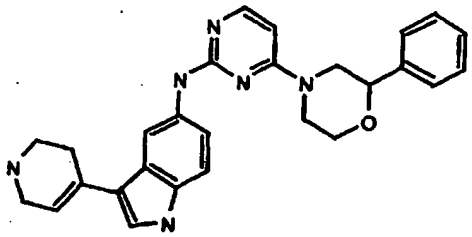
$N^4$-Methyl-$N^4$-(2-pyridin-2-yl-ethyl)-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine



The title compound was made in a 1% yield in a manner described in Example 9. It was characterized as a white solid isolated as its free base after purifying the TFA salt over silica (93:7:0.7 $CHCl_3$:$CH_3OH$:$NH_4OH$). $C_{25}H_{27}N_7$. MS: 426.1 (MH+); $^1$H NMR ($CD_3OD$) δ 8.37 (s, 1 H), 8.00 (s, 1 H), 7.76 (t, *J = 7.5 Hz*, 1 H), 7.44 (bs, 1 H), 7.33-7.15 (m, 5 H), 6.14 (s, 1 H), 5.97 (d, *J = 5.8 Hz*, 1 H), 5.94 (d, *J = 7.5 Hz*, 1 H), 3.87-3.78 (m, 2 H), 3.52-3.50 (m, 2 H), 3.11-3.06 (m, 2 H), 3.00 (s, 3 H), 2.97 (s, 2 H) ppm.

Example 54

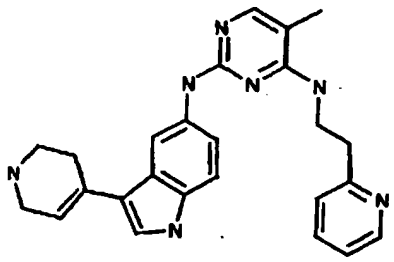
[4-(2-Phenyl-morpholin-4-yl)-pyrimidin-2-yl]-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-amine



The title compound was synthesized in a 9% overall yield in a manner described by Example 9 using 2-phenylmorpholine and 2,4-dichloropyrimidine. It was characterized as an off-white solid isolated as its TFA salt. $C_{27}H_{28}N_6O$. MS: 453.3 (MH+); $^1H$ NMR

Example 55

5-Methyl-$N^4$-(2-pyridin-2-yl-ethyl)-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine

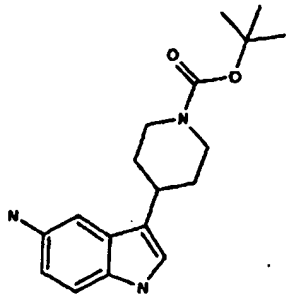


$C_{25}H_{27}N_7$.

Example 56

5-Bromo-$N^2$-(3-piperidin-4-yl-1H-indol-5-yl)-$N^4$-(2-pyridin-2-yl-ethyl)-pyrimidine-2,4-diamine

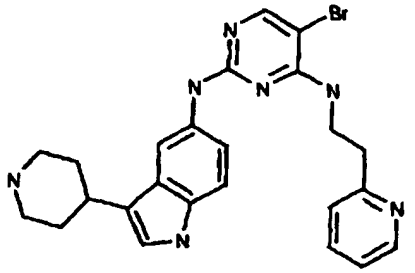
A. 4-(5-Amino-1H-indol-3-yl)-piperidine-1-carboxylic acid tert-butyl ester



5.00 g 4-(5-Nitro-1H-indol-3-yl)-3,6-dihydro-2H-pyridine-1-carboxylic acid tert-butyl ester (14.6 mmol) was taken into 40.0 mL THF and 160 mL ethyl acetate 2/ 1.00 mL (5.74 mmol) diisopropylethylamine. 1.56 g (1.46 mmol) Pd/C was added. The reaction was shaken on a parr shaker under 3 atm $H_2$ for 90 minutes. The reaction vessel was removed from pressure. It was filtered through a bed of diatomaceous earth and was washed thoroughly with ethyl acetate. The clear, colorless filtrate was evaporated under reduced pressure to give an impure white solid. The white solid was taken into a minimum amount of dichloromethane and tritrated with hexanes. Filtration afforded the title copound in 84% yield as a white solid. $C_{18}H_{25}N_3O_2$. MS: 315.3, 216.1 (MH+); $^1$H NMR ($D_6$-DMSO) δ 10.24 (s, 1 H), 6.99 (d, *J = 8.3 Hz*, 1 H), 6.87 (d, *J = 2.1 Hz*, 1 H), 6.66 (s, 1 H), 6.42 (dd, *J = 2.1 Hz, 8.3 Hz*, 1 H), 4.38 (s, 2 H), 4.00 (m, 2 H), 2.75 (m, 2 H), 2.47 (m, 2 H), 1.86 (m, 2 H), 1.46 (m, 2 H) ppm.

B. 5-Bromo-$N^2$-(3-piperidin-4-yl-1H-indol-5-yl)-$N^4$-(2-pyridin-2-yl-ethyl)-pyrimidine-2,4-diamine

The title compound was made in a manner similar to Example 1D and deprotected according to the procedure of Example 1 E in a 38% yield. The compound was characterized as an off-white solid and isolated as its HCl salt.



$C_{24}H_{26}BrN_7$. MS: 492.1/494.0 (MH+); $^1$H NMR ($D_6$-DMSO) δ 11.11 (s, 1 H), 10.57 (s, 1 H), 9.16 (s, 1 H), 9.08 (s, 1 H), 8.69 (s, 1 H), 8.61 (s, 1 H), 8.32 (bs, 1 H), 8.17 (bs, 1 H), 7.74 (s, 2 H), 7.37 (d, *J = 8.7 Hz*, 1 H), 7.15 (s, 1 H), 7.11 (s, 1 H), 3.73 (s, 2 H), 3.26 (s, 4 H), 2.02 (s, 2 H), 1.88 (s, 2 H) ppm.

## Example 57

5-Bromo-$N^2$-(1-methanesulfonyl-3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl)-$N^4$-(2-pyridin-2-yl-ethyl)-pyrimidine-2,4-diamine

A. 4-(1-Methanesulfonyl-5-nitro-1H-indol-3-yl)-3,6-dihydro-2H-pyridine-1-carboxylic acid tert-butyl ester

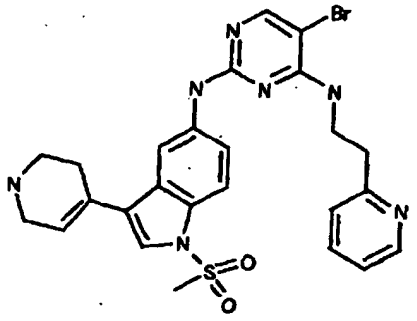
2.00 g (5.82 mmol) 4-(5-Nitro-1H-indol-3-yl)-3,6-dihydro-2H-pyridine-1-carboxylic acid tert-butyl ester was suspended in 15.0 mL toluene and 15.0 mL 15% sodium hydroxide solution and cooled to 0° C. To this was added 349 mg (0.874 mmol) $^n$bu$_4$N(HSO$_4$) tetra-n-butyl hydrogensulfate. 676 □L (8.74 mmol) methanesulfonyl chloride was slowly dropped in. There was noted an immediate dissolution of the solids and a color change to red. Allowed

the reaction to slowly warm to ambient temperature over sixteen hours. Reaction was regularly monitored and aliquots of 676 ΠL (8.74 mmol) methanesulfonyl chloride were added until complete disappearance of starting material by TLC. Ethyl acetate was added and the layers were separated. Aqueous work-up gave a yellow solid which was purified over silica (20%→ 50% ethyl acetate in hexanes) to give the title compound in a 76% yield as a yellow solid. $^1$H NMR ($D_6$-DMSO) δ 8.69 (d, *J = 2.3 Hz*, 1 H), 8.25 (dd, *J = 9.1,2.3 Hz*, 1 H), 8.05 (d, *J = 9.1 Hz*, 1 H), 7.84 (s, 1 H), 6.34 (s, 1 H), 4.06 (s, 2 H), 3.56 (s, 3 H), 3.55-3.53 (m, 2 H), 2.51 (s, 2 H), 1.41 (s, 9 H) ppm.

B. 4-(5-Amino-1-methanesulfonyl-1H-indol-3-yl)-3,6-dihydro-2H-pyridine-1-carboxylic acid tert-butyl ester

4-(1-Methanesulfonyl-5-nitro-1H-indol-3-yl)-3,6-dihydro-2H-pyridine-1-carboxylic acid tert-butyl ester was reduced in a manner described in Example 1C in a 89% yield as an orange foam. $^1$H NMR ($D_6$-DMSO) δ 7.48 (d, *J = 9.0 Hz*, 1 H), 7.33 (s, 1 H), 7.05 (s, 1 H), 6.66 (d, *J = 9.0 Hz*, 1 H), 6.16 (s, 1 H), 4.98 (s, 2 H), 4.02-3.96 (m, 2 H), 3.53-3.50 (m, 2 h), 3.23 (s, 3 H), 2.47-2.44 (m, 2 H), 1.40 (s, 9 H) ppm.

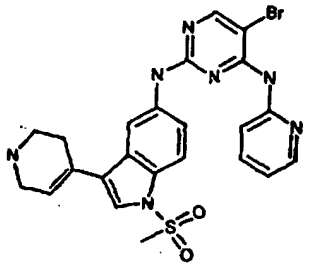
C. 5-Bromo-$N^2$-[1-methanesulfonyl-3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-$N^4$-(2-pyridin-2-yl-ethyl)-pyrimidine-2,4-diamine



The title compound was made in a manner 30% yield in a manner described in Example 1D and 1E. It was characterized as an off-white solid and isolated as its HCl salt. $C_{25}H_{26}BrN_7O_2S$. MS: 568.0/569.9 (MH+); $^1$H NMR ($D_6$-DMSO) δ 10.67 (bs, 1 H), 9.52 (s, 2 H), 8.64 (d, *J = 5.4 Hz*, 1 H), 8.44 (s, 1 H), 8.27 (s, 1 H), 8.18 (s, 2 H), 7.86 (d, *J = 9.0 Hz*, 1 H), 7.75-7.67 (m, 2 H), 7.52 (d, *J = 9.0 Hz*, 1 H), 6.29 (s, 1 H), 3.77 (s, 2 H), 3.48 (s, 3 H), 3.28 (s, 4 H), 2.73 (s, 2 H) ppm.

Example 58

5-Bromo-$N^2$-[1-methanesulfonyl-3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-$N^4$-pyridin-2-yl-pyrimidine-2,4-diamine



$C_{23}H_{22}BrN_7O_2S$.

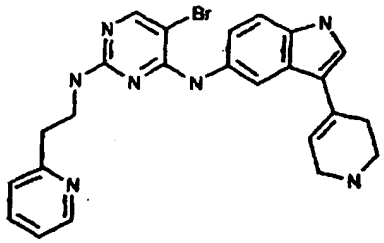
Example 59

5-Bromo-$N^2$-(2-pyridin-2-yl-ethyl)-$N^4$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine

A. (5-Bromo-2-chloro-pyrimidin-4-yl)-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-amine

The title compound was made in a quantitative yield following the procedure of Example 1A. It was characterized as an oily, yellow solid without purification. $C_{17}H_{15}BrClN_5$ MS: 503.1/505.1 (MH+); $^1$H NMR ($CD_3OD$) δ 8.23 (s, 1 H), 8.14 (s, 1 H), 7.35 (d, *J = 8.5 Hz*, 1 H), 7.30 (s, 1 H), 7.22 (d, *J = 8.5 Hz*, 1 H), 6.14 (s, 1 H), 4.10 (s, 2 H), 3.64 (s, 2 H), 2.56 (s, 2 H), 1.48 (s, 9 H) ppm.

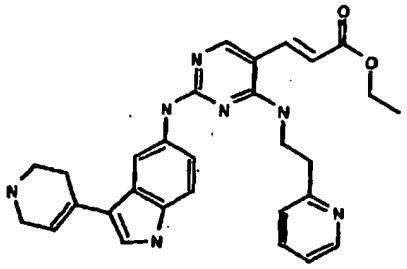
B. 5-Bromo-$N^2$-(2-pyridin-2-yl-ethyl)-$N^4$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine



The title compound was made in a 2% yield via the manner described in Example 1D and 1E. It was characterized as an off white solid isolated as its free base after purifying the HCl salt over silica (93:7:0.7 $CHCl_3$:$CH_3OH$:$NH_4OH$). $C_{24}H_{24}BrN_7$. HPLC ret. time: 3.93 min.; MS: 490.0/492.1 (MH+); $^1$H NMR ($CD_3OD$) δ 8.31 (s, 1 H), 7.94 (bs, 1 H), 7.87 (s, 1 H), 7.37-7.32 (m, 4 H), 7.26 (dt, *J = 9.0, 2.0 Hz*, 1 H), 7.12 (s, 1 H), 6.16 (s, 1 H), 3.67 (s, 2 H), 3.43 (s, 2 H), 3.25-3.24 (m, 2 H), 2.84 (s, 2 H), 2.67 (s, 2 H) ppm.

Example 60

3-{4-[2-Pyridin-2-yl-ethylamino)-2-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-ylamino]-pyrimidin-5-yl}-acrylic acid ethyl ester



$C_{29}H_{31}N_7O_2$.

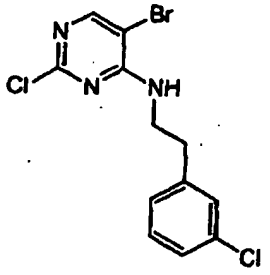
Example 60A

5-{5-Bromo-4-[2-(3-chloro-phenyl)-ethylamino]-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one

Example 61

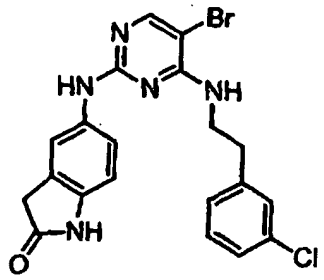
5-Bromo-$N^4$-[2-(3-chloro-phenyl)-ethyl]-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine

A. (5-Bromo-2-chloro-pyrimidin-4-yl)-[2-(3-chloro-phenyl)-ethyl]-amine ($C_{12}H_{10}BrCl_2N_3$)



Using method B, the title compound was isolated in a 79% yield (1.37 g, 3.95 mmol) as a white solid. GC/MS: ret. time = 5.30, m/z 345/347/349; $^1$H NMR ($d_6$-DMSO) δ 8.20 (s, 1H), 7.75 (t, 1H), 7.29-7.12 (m, 4H), 3.56 (q, 2H), 2.84 (t, 2H) ppm.

B. 5-[5-Bromo-4-[2-(3-chloro-phenyl)-ethylamino]-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one ($C_{20}H_{17}BrClN_5O$)

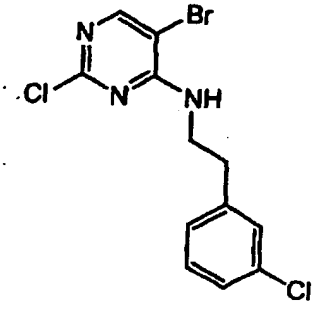


The title compound was isolated as a brown solid in a 14% yield. MS: 459.9/461.2 (MH+). $^1$H NMR ($d_6$-DMSO) δ: 10.19 (s, 1H), 9.02 (s, 1H), 8.28 (s, 1H), 7.93 (s, 1H), 7.41 (dd, 1H), 7.30-7.22 (m, 3H), 7.13-7.11 (m, 1H), 6.98 (t, 1H), 6.65 (d, 1H), 3.56 (q, 2H), 3.33 (s,1H), 2.84 (t, 2H).

Example 62

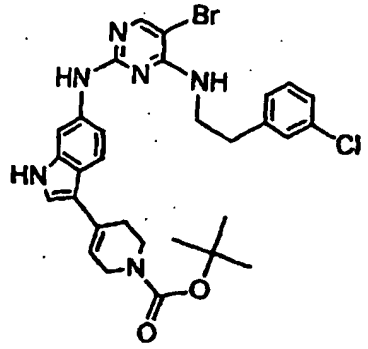
5-Bromo-$N^4$-[2-(3-chloro-phenyl)-ethyl]-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine

A. (5-Bromo-2-chloro-pyrimidin-4-yl)-[2-(3-chloro-phenyl)-ethyl]-amine



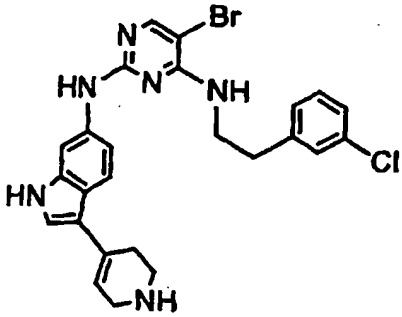
The title compound was prepared according to method b and isolated in a 79% yield (1.37 g, 3.95 mmol) as a white solid ($C_{12}H_{10}BrCl_2N_3$): GC/MS: ret. time = 5.30, m/z 345/347/349; $^1$H NMR ($d_6$-DMSO) δ 8.20 (s, 1H), 7.75 (t, 1H), 7.29-7.12 (m, 4H), 3.56 (q, 2H), 2.84 (t, 2H) ppm.

B. 4-{6-[5-Bromo-4-[2-(3-chloro-phenyl)-ethylamino]-pyrimidin-2-ylamino}-1H-indol-3-yl)-3,6-dihydro-2H-pyridine-1-carboxylic acid tert-butyl ester.



The title compound was prepared according to method E ($C_{30}H_{32}BrClN_6O_2$): MS: 623.1/625.1 (MH+); $^1$H NMR ($d_6$-DMSO) δ: 10.99 (s, 1H), 8.92 (s, 1H), 8.12 (s, 1H), 7.94 (s, 1H), 7.40-7.33 (m, 2H), 7.24-7.16 (m, 4H), 7.02-7.00 (m, H), 6.92 (t, 1H), 6.02 (s, 1H), 3.94 (s, 2H), 3.56 (q, 2H), 3.46 (m, 2H), 3.28 (s, 1H), 2.81 (t, 2H), 1.38 (s, 9H) ppm.

C. 5-Bromo-$N^4$-[2-(3-chloro-phenyl)-ethyl]-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine ($C_{25}H_{24}BrClN_6$).

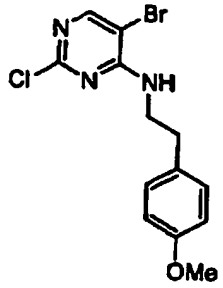


The title compound was prepared according to method G and isolated as the TFA salt in a 15% yield. MS: 522.9/525.1 (MH+). $^1$H NMR ($CDCl_3$) δ: 12.16 (s, 1H), 9.67 (s, 2H), 8.90 (s, 1H), 8.75 (s, 2H), 8.34 (s, 1H), 8.19-8.13 (m, 2H), 8.03-7.94 (m, 3H), 7.72 (s, 1H), 6.87 (s, 1H), 4.51 (s, 2H), 4.32 (s, 2H), 4.07 (s, 2H), 3.59 (s, 2H), 3.47 (s, 2H) ppm.

Example 63

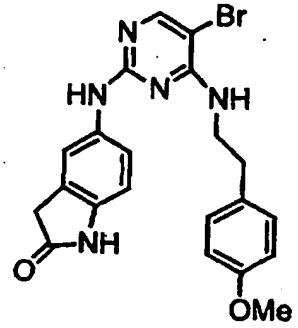
5-[5-Bromo-4-[2-(4-methoxy-phenyl)-ethylamino]-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one

A. (5-Bromo-2-chloro-pyrimidin-4-yl)-[2-(4-methoxy-phenyl)-ethyl]-amine.



The title compound was prepared according to method b and isolated as a light yellow, viscous oil in an 80% yield ($C_{13}H_{13}BrClN_3O$). GC/MS: ret. time = 5.45. MS: 342.1/344.1/384.1 (MH+). $^1$H NMR ($d_6$-DMSO) δ: 8.18 (s, 1H), 7.70 (t, 1H), 7.09 (d, 2H), 6.81 (d, 2H), 3.67 (s, 3H), 3.50 (q, 2H), 2.75 (t, 2H) ppm.

B. 5-[5-Bromo-4-[2-(4-methoxy-phenyl)-ethylamino]-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one ($C_{21}H_{20}BrN_5O_2$).

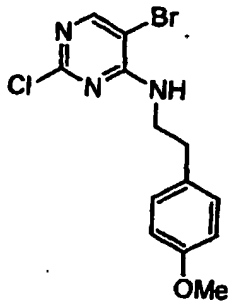


The title compound was prepared according to method E and isolated as a pink solid in a 40% yield. MS: 454.1/456.0 (MH+). $^1$H NMR ($d_6$-DMSO) δ: 10.22 (s, 1H), 9.01 (s, 1H), 7.93 (s, 1H), 7.51 (s, 1H), 7.44 (d, 1H), 7.07 (d, 2H), 6.95 (t, 1H), 6.81 (d, 2H), 6.65 (d, 2H), 3.69 (s, 3H), 3.52 (q, 2H), 3.30 (s, 2H), 2.74 (t, 2H) ppm.

Example 64

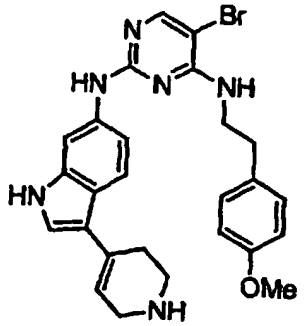
5-Bromo-$N^4$-[2-(4-methoxy-phenyl)-ethyl]-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine

A. (5-Bromo-2-chloro-pyrimidin-4-yl)-[2-(4-methoxy-phenyl)-ethyl]-amine ($C_{13}H_{13}BrClN_3O$)



The title compound was isolated as a light yellow, viscous oil in an 80% yield. GC/MS: ret. time = 5.45 min. MS: 342.1/344.1/364.1 (MH+). $^1$H NMR ($d_6$-DMSO) δ: 8.18 (s, 1H), 7.70 (t, 1H), 7.09 (d, 2H), 6.81 (d, 2H), 3.67 (s, 3H), 3.50 (q, 2H), 2.75 (t, 2H) ppm.

B. 5-Bromo-$N^4$-[2-(4-methoxy-phenyl)-ethyl]-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine ($C_{25}H_{27}BrN_6O$).

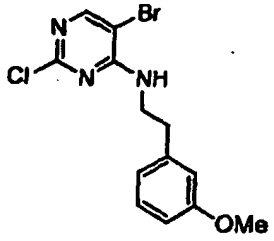


The title compound was isolated as a tan solid in the TFA salt form in a 6.6% yield. MS: 520.4/522.3 (MH+). $^1$H NMR ($d_6$-DMSO) δ: 11.36 (s, 1H), 8.80, (s, 2H), 8.07 (s, 1H), 7.94 (s, 1H), 7.56 (s, 1H), 7.38-7.32 (m, 2H), 6.83 (s, 2H), 6.65 (s, 2H), 6.06 (s, 1H), 3.68-3.25 (m, 10H), 2.66 (s, 4H) ppm.

Example 65

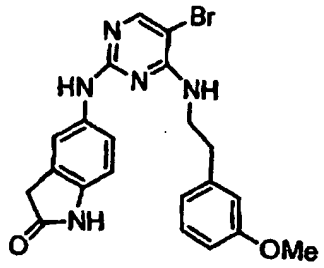
5-(5-Bromo-4-[2-(3-methoxy-phenyl)-ethylamino]-pyrimidin-2-ylamino)-1,3-dihydro-indol-2-one

A. (5-Bromo-2-chloro-pyrimidin-4-yl)-[2-(3-methoxy-phenyl)-ethyl]-amine ($C_{13}H_{13}BrClN_3O$)



The title intermediate compound was isolated as a colorless oil in an 84% yield. GC/MS: ret. time = 5.39 min, m/z = 341/343/345. $^1$H NMR ($d_6$-DMSO) δ: 8.19 (s, 1H), 7.72 (t, 1H), 7.16 (t, 1H), 6.76-6.72 (m, 3H), 3.70 (s, 3H), 3.55 (q, 2H), 2.79 (t, 2H) ppm.

B. 5-(5-Bromo-4-[2-(3-methoxy-phenyl)-ethylamino]-pyrimidin-2-ylamino)-1,3-dihydro-indol-2-one ($C_{21}H_{20}BrN_5O_2$)

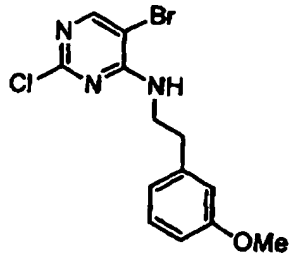


The title compound was isolated as a light pink solid in a 67% yield. MS: 454.1/456.1 (MH+). $^1$H NMR ($d_6$-DMSO) δ: 10.17 (s, 1H), 9.01 (s, 1H), 7.93 (s, 1H), 7.54 (s, 1H), 7.41 (1H), 7.17 (t, 1H), 6.95 (t, 1H), 6.76-6.72 (m, 3H), 6.64 (d, 1H), 3.68 (s, 3H), 3.56 (q, 2H), 3.31 (s, 2H), 2.80 (t, 2H) ppm.

Example 66

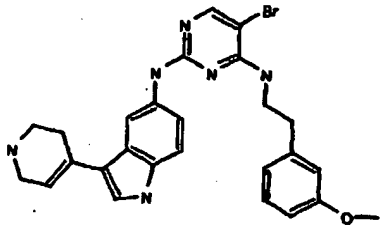
5-Bromo-$N^4$-[2-(3-methoxy-phenyl)-ethyl]-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine

A. (5-Bromo-2-chloro-pyrimidin-4-yl)-[2-(3-methoxy-phenyl)-ethyl]-amine ($C_{13}H_{13}BrClN_3O$)



The title intermediate compound was isolated as a colorless oil in an 84% yield. GC/MS: ret. time = 5.39 min, m/z = 341/343/345. $^1$H NMR ($d_6$-DMSO) δ: 8.19 (s, 1H), 7.72 (t, 1H), 7.16 (t, 1H), 6.76-6.72 (m, 3H), 3.70 (s, 3H), 3.55 (q, 2H), 2.79 (t, 2H) ppm.

B. 5-Bromo-$N^4$-[2-(3-methoxy-phenyl)-ethyl]-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine ($C_{26}H_{27}BrN_6O$)

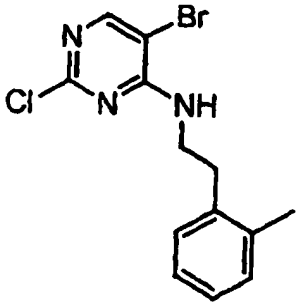


The title compound was isolated as a tan solid in the TFA salt form in a 16% yield. MS: 519.2/521.1 (MH+). $^1$H NMR ($d_6$-DMSO) δ: 11.45 (s, 1H), 8.82 (s, 2H), 8.08 (s, 1H), 8.00 (s, 1H), 7.56 (s, 1H), 7.38 (s, 2H), 7.10 (t, 1H), 6.77-6.63 (m, 3H), 6.10 (s, 1H), 3.72-3.28 (m, 10H), 2.82-2.80 (m, 2H), 2.70 (s, 2H) ppm.

Example 67

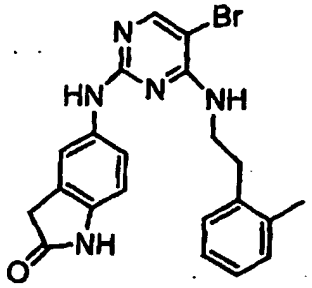
5-[5-Bromo-4-(2-o-tolyl-ethylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one

A. (5-Bromo-2-chloro-pyrimidin-4-yl)-(2-o-tolyl-ethyl)-amine ($C_{13}H_{13}BrClN_3$)



The title intermediate was isolated as a white solid in a 79% yield. MS: 324.2/326.0/328.1 (MH-). $^1$H NMR ($d_6$-DMSO) δ: 8.25 (s, 1H), 7.91 (t, 1H), 7.18-7.10 (m, 4H), 3.56-3.51 (m, 2H), 2.88-2.82 (m, 2H), 2.37 (s, 1H) ppm.

B. 5-[5-Bromo-4-(2-o-tolyl-ethylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one ($C_{21}H_{20}BrN_5O$).

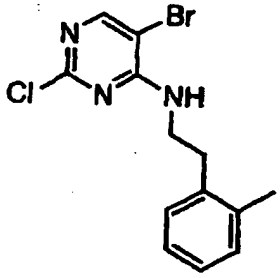


The title compound was isolated as a grey solid in a 28% yield. MS: 438.1/440.0 (MH+). $^1$H NMR ($d_6$-DMSO) δ: 10.20 (s, 1H), 9.03 (s, 1H), 7.97 (s, 1H), 7.56 (s, 1H), 7.46 (dd, 1H), 7.13-7.04 (m, 5H), 6.67 (d, 1H), 3.59-3.54 (m, 2H), 3.33 (s, 2H), 2.84 (t, 2H), 2.26 (s, 3H).

Example 68

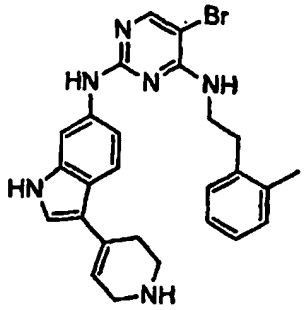
5-Bromo-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-$N^4$-(2-o-tolyl-ethyl)-pyrimidine-2,4-diamine

A. (5-Bromo-2-chloro-pyrimidin-4-yl)-(2-o-tolyl-ethyl)-amine ($C_{13}H_{13}BrClN_3$)



The title intermediate was isolated as a white solid in a 79% yield. MS: 324.2/326.0/328.1 (MH-). $^1$H NMR ($d_6$-DMSO) δ: 8.25 (s, 1H), 7.91 (t, 1H), 7.18-7.10 (m, 4H), 3.56-3.51 (m, 2H), 2.88-2.82 (m, 2H), 2.37 (s, 1H) ppm.

B. 5-Bromo-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-$N^4$-(2-o-tolyl-ethyl)-pyrimidine-2,4-diamine ($C_{26}H_{27}BrN_6$).

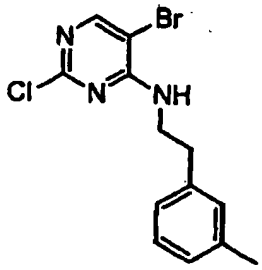


The title compound was isolated in the TFA salt form as a light yellow solid in a 21% yield. HPLC ret. time = 5.53 min. MS: 502.9/505.1 (MH+). $^1$H NMR ($d_6$-DMSO) δ: 11.36 (s, 1H), 8.82 (s, 2H), 8.10 (s, 1H), 7.98 (s, 1H), 7.57 (d, 1H), 7.40-7.32 (m, 2H), 7.08 (m, 2H), 6.95 (m, 2H), 6.09 (s, 1H), 3.70-3.27 (m, 7H), 2.79-2.70 (m, 4H), 2.16 (s, 3H) ppm.

Example 69

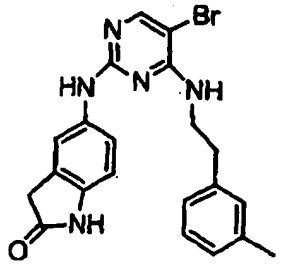
5-[5-Bromo-4-(2-m-tolyl-ethylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one

A. (5-Bromo-2-chloro-pyrimidin-4-yl)-(2-m-tolyl-ethyl)-amine ($C_{13}H_{13}BrClN_3$).



The title intermediate was isolated as a white solid in a 77% yield. MS: 326.1/328.1/330.1 (MH+). $^1$H NMR ($d_6$-DMSO) δ: 8.25 (s, 1H), 7.79 (t, 1H), 7.19 (t, 1H), 7.05-7.00 (m, 3H), 3.61-3.54 (m, 2H), 2.82 (t, 2H), 2.29 (s, 3H) ppm.

B. 5-[5-Bromo-4-(2-m-tolyl-ethylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one ($C_{21}H_{20}BrN_5O$).



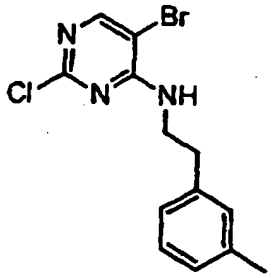
The title compound was isolated as a light pink solid in a 41% yield. MS: 438.1/440.0 (MH+). $^1$H NMR ($d_6$-DMSO) δ: 10.24 (s, 1H), 9.06 (s, 1H), 7.97 (s, 1H), 7.56 (s, 1H), 7.50 (d,

1H), 7.20-7.15 (m, 1H), 7.04-6.98 (m, 3H), 6.68 (d, 1H), 3.58 (q, 2H), 3.33 (s, 2H), 2.82 (t, 2H), 2.27 (s, 3H) ppm.

Example 70

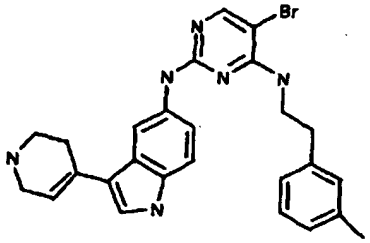
5-Bromo-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-$N^4$-(2-m-tolyl-ethyl)-pyrimidine-2,4-diamine

A. (5-Bromo-2-chloro-pyrimidin-4-yl)-(2-m-tolyl-ethyl)-amine ($C_{13}H_{13}BrClN_3$).



The title intermediate was isolated as a white solid in a 77% yield. MS: 326.1/328.1/330.1 (MH+). $^1$H NMR ($d_6$-DMSO) δ: 8.25 (s, 1H), 7.79 (t, 1H), 7.19 (t, 1H), 7.05-7.00 (m, 3H), 3.61-3.54 (m, 2H), 2.82 (t, 2H), 2.29 (s, 3H) ppm.

B. 5-Bromo-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-$N^4$-(2-m-tolyl-ethyl)-pyrimidine-2,4-diamine ($C_{28}H_{27}BrN_8$).

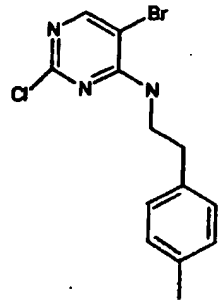


The title compound was isolated as a light yellow solid in a 21% yield. HPLC ret. time = 5.61 min. MS: 503.2/505.2 (MH+). $^1$H NMR ($d_6$-DMSO) δ: 11.36 (s, 1H), 8.83 (s, 2H), 8.10 (s, 1H), 7.99 (s, 1H), 7.56 (s, 1H), 7.39 (s, 2H), 7.10-6.83 (m, 4H), 6.09 (s, 1H), 3.72 (s, 2H), 3.53 (s, 2H), 3.27 (s, 3H), 2.79-2.69 (m, 4H), 2.19 (s, 3H) ppm.

Example 71

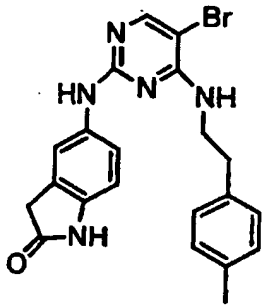
5-[5-Bromo-4-(2-p-tolyl-ethylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one

A. (5-Bromo-2-chloro-pyrimidin-4-yl)-(2-p-tolyl-ethyl)-amine ($C_{13}H_{13}BrClN_3$).



The title intermediate was isolated as a white solid in a 73% yield. MS: 326.1/328.0/330.0 ($MH^+$). $^1H$ NMR ($d_6$-DMSO) δ: 8.23 (s, 1H), 7.76 (t, 1H), 7.10 (s, 4H), 3.56 (q, 2H), 2.82 (t, 2H), 2.27 (s, 3H) ppm.

B. 5-[5-Bromo-4-(2-p-tolyl-ethylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one ($C_{21}H_{20}BrN_5O$).

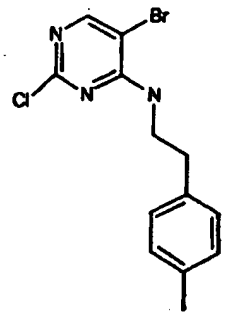


The title compound was isolated as a brown solid in a 14% yield. MS: 438.1/440.0/ ($MH^+$). $^1H$ NMR ($d_6$-DMSO) δ: 10.22 (s, 1H), 9.05 (s, 1H), 7.97 (s, 1H), 7.55 (s, 1H), 7.48 (dd, 1H), 7.09 (s, 1H), 6.99 (t, 1H), 6.69 (d, 1H), 4.03 (q, 2H), 3.33 (s, 2H), 2.81 (t, 2H), 2.23 (s, 3H) ppm.

Example 72

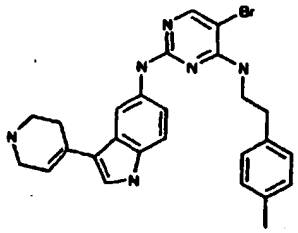
5-Bromo-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-$N^4$-(2-p-tolyl-ethyl)-pyrimidine-2,4-diamine

A. (5-Bromo-2-chloro-pyrimidin-4-yl)-(2-p-tolyl-ethyl)-amine ($C_{13}H_{13}BrClN_3$).



The title intermediate was isolated as a white solid in a 73% yield. MS: 326.1/328.0/330.0 (MH+). $^1$H NMR ($d_6$-DMSO) δ: 8.23 (s, 1H), 7.76 (t, 1H), 7.10 (s, 4H), 3.56 (q, 2H), 2.82 (t, 2H), 2.27 (s, 3H) ppm.

B. 5-Bromo-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-$N^4$-(2-p-tolyl-ethyl)-pyrimidine-2,4-diamine ($C_{26}H_{27}BrN_6$).

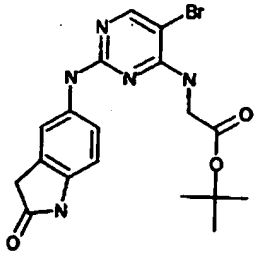


The title compound was isolated as a yellow solid in the TFA salt form in a 13% yield. MS: 503.1/504.1 (MH+). $^1$H NMR ($d_6$-DMSO) δ: 11.34 (s, 1H), 8.77 (s, 2H), 8.05 (s, 1H), 7.95 (s, 1H), 7.54 (s, 1H), 7.35 (s, 2H), 6.94-6.87 (m, 4H), 6.06 (s, 1H), 3.68 (s, 4H), 3.46 (m, 2H), 3.24 (s, 2H), 2.66 (s, 3H), 2.21 (s, 3H) ppm.

Example 73

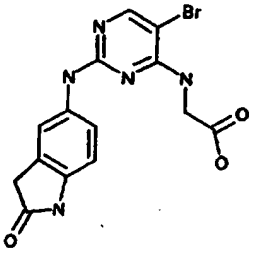
[5-Bromo-2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-pyrimidin-4-ylamino]-acetic acid

A. [5-Bromo-2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-pyrimidin-4-ylamino]-acetic acid tert-butyl ester ($C_{18}H_{20}BrN_5O_3$).



The title intermediate was isolated as a light yellow solid in a 3.5% yield. MS: 434.1/436.1 (MH+). $^1$H NMR ($d_6$-DMSO) δ: 10.18 (s, 1H), 9.05 (s, 1H), 7.98 (s, 1H), 7.43-7.42 (m, 2H), 7.18 (t, 1H), 6.65 (d, 1H), 3.95 (d, 2H), 3.39 (s, 2H), 1.29 (s, 9H) ppm.

B. [5-Bromo-2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-pyrimidin-4-ylamino]-acetic acid ($C_{14}H_{12}BrN_5O_3$).

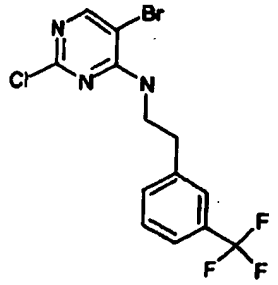


The title compound was isolated as a brown solid. No yield determined. MS: 377.9/380.2 (MH+). $^1$H NMR ($d_6$-DMSO) δ: 10.21 (s, 1H), 9.10 (s, 1H), 8.02 (s, 1H), 7.59 (s, 1H), 7.38 (dd, 1H), 7.19 (t, 1H), 6.69 (d, 1H), 3.99 (d, 2H), 3.42 (s, 2H) ppm.

Example 74

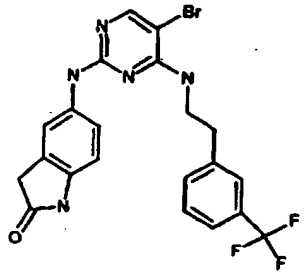
5-{5-Bromo-4-[2-(3-trifluoromethyl-phenyl)-ethylamino]-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one

A. (5-Bromo-2-chloro-pyrimidin-4-yl)-[2-(3-trifluoromethyl-phenyl)-ethyl]-amine ($C_{13}H_{10}BrClF_3N_3$).



The title intermediate was isolated as a white solid in an 84% yield. GC/MS: ret time = 4.65 min, m/z = 379/381/383. $^1$H NMR ($d_6$-DMSO) δ: 8.25 (s, 1H), 7.80 (t, 1H), 7.65-7.52 (m, 4H), 3.65 (q, 2H), 2.98 (t, 2H) ppm.

B. 5-{5-Bromo-4-[2-(3-trifluoromethyl-phenyl)-ethylamino]-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one ($C_{21}H_{17}BrF_3N_5O$).

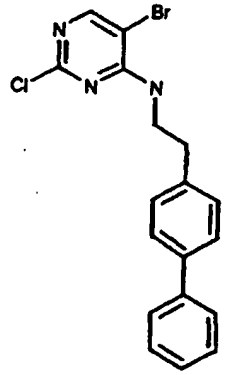


The title compound was isolated as a pink solid in a 37% yield. MS: 492.2/493.5 (MS+). $^1$H NMR ($d_6$-DMSO) δ: 10.18 (s, 1H), 9.00 (s, 1H), 7.93 (s, 1H), 7.54-7.47 (m, 5H), 7.39 (dd, 1H), 6.96 (t, 1H), 6.63 (d, 1H), 3.60 (q, 2H), 3.35 (s, 2H), 2.95 (t, 2H) ppm.

Example 75

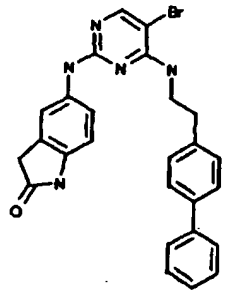
5-[4-(2-Biphenyl-4-yl-ethylamino)-5-bromo-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one

A. (2-Biphenyl-4-yl-ethyl)-(5-bromo-2-chloro-pyrimidin-4-yl)-amine ($C_{18}H_{15}BrClN_3$).



The title intermediate was isolated as a white solid in a 74% yield. GC/MS: ret. time = 6.94; m/z = 387/389/391. $^1$H NMR ($d_6$-DMSO) δ: 8.24 (s, 1H), 7.83 (t, 1H), 7.65-7.58 (m, 4H), 7.45 (t, 2H), 7.33 (m, 3H), 3.62 (q, 2H), 2.90 (t, 2H) ppm.

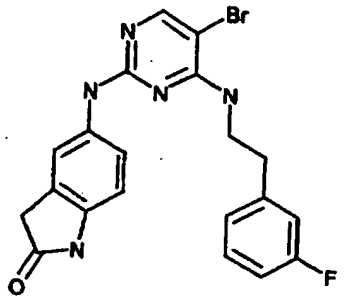
B. 5-[4-(2-Biphenyl-4-yl-ethylamino)-5-bromo-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one ($C_{26}H_{22}BrN_5O$)



The title compound was isolated as a gray solid in an 11% yield. MS: 500.1/502.3 (MH+). $^1$H NMR ($d_6$-DMSO) δ: 10.25 (s, 1H), 9.07 (s, 1H), 7.99 (s, 1H), 7.68-7.29 (m, 11H), 7.07 (t, 1H), 6.72 (d, 1H), 3.64 (q, 2H), 3.39 (s, 2H), 2.91 (t, 2H) ppm.

Example 76

5-[5-Bromo-4-[2-(3-fluoro-phenyl)-ethylamino]-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one ($C_{20}H_{17}BrFN_5O$).

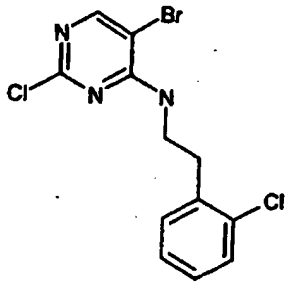


The title compound was isolated as a pink solid in a 52% yield. MS: 442.2/444.1 (MH+). $^1$H NMR ($d_6$-DMSO) δ: 10.22 (s, 1H), 9.05 (s, 1H), 7.98 (s, 1H), 7.57 (s, 1H), 7.45 (dd, 1H), 7.38-7.30 (m, 1H), 7.08-7.00 (m, 4H), 6.69 (d, 1H), 3.62 (q, 2H), 3.37 (s, 2H), 2.91 (t, 2H) ppm.

Example 77

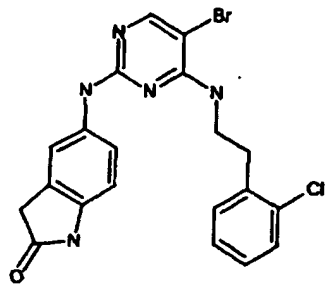
5-[5-Bromo-4-[2-(2-chloro-phenyl)-ethylamino]-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one

A. (5-Bromo-2-chloro-pyrimidin-4-yl)-[2-(2-chloro-phenyl)-ethyl]-amine ($C_{12}H_{10}BrCl_2N_3$).



The title intermediate was isolated as a white solid in an 87% yield. GC/MS: ret. Time = 5.22 min; m/z: 345/347/349. $^1$H NMR ($d_6$-DMSO) δ: 8.19 (s, 1H), 7.80 (t, 1H), 7.39-7.35 (m, 1H), 7.27-7.18 (m, 3H), 3.59 (q, 2H), 2.96 (t, 2H) ppm.

B. 5-{5-Bromo-4-[2-(2-chloro-phenyl)-ethylamino]-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one ($C_{20}H_{17}BrClN_5O$).

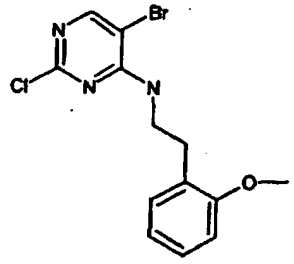


The title compound was isolated as pink solid in a 47% yield. MS: 458.1/460.0/462.1 (MH+). $^1$H NMR ($d_6$-DMSO) δ: 10.17 (s, 1H), 8.99 (s, 1H), 7.93 (s, 1H), 7.51 (s, 1H), 7.43-7.40 (m, 2H), 7.40-7.20 (m, 3H), 7.01 (t, 1H), 6.63 (d, 1H), 3.60 (q, 2H), 3.30 (s, 2H), 2.97 (t, 2H) ppm.

Example 78

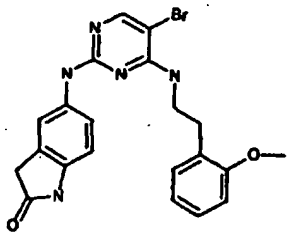
5-{5-Bromo-4-[2-(2-methoxy-phenyl)-ethylamino]-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one

A. (5-Bromo-2-chloro-pyrimidin-4-yl)-[2-(2-methoxy-phenyl)-ethyl]-amine ($C_{13}H_{13}BrClN_3O$).



The title intermediate was isolated as a white solid in a 77% yield. GC/MS: ret. Time = 5.26 min; m/z: 341/343/345. $^1$H NMR ($d_6$-DMSO) δ: 8.17 (s, 1H), 7.63 (t, 1H), 7.17-7.13 (m, 1H), 7.07 (dd, 1H), 6.93-6.90 (m, 1H), 6.83-6.79 (m, 1H), 3.75 (s, 3H), 3.53 (q, 2H), 2.81 (t, 2H) ppm.

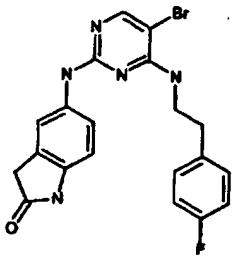
B. 5-[5-Bromo-4-[2-(2-methoxy-phenyl)-ethylamino]-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one ($C_{21}H_{20}BrN_5O_2$).



The title compound was isolated as a light pink solid in a 44% yield. MS: 454.1/456.0 (MH+). $^1$H NMR ($d_6$-DMSO) δ: 10.16 (s, 1H), 8.99 (s, 1H), 7.92 (s, 1H), 7.53 (s, 1H), 7.43 (dd, 1H), 7.20-7.15 (m, 1H), 7.09-7.07 (m, 1H), 6.94-6.92 (m, 1H), 6.87-6.81 (m, 2H), 6.62 (d, 1H), 3.73 (s, 3H), 3.54 (q, 2H), 2.83 (t, 2H) ppm.

Example 79

5-[5-Bromo-4-[2-(4-fluoro-phenyl)-ethylamino]-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one ($C_{20}H_{17}BrFN_5O$).

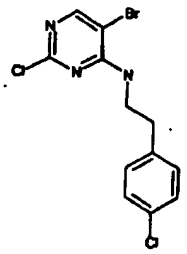


The title compound was isolated as a pink solid in a 44% yield. MS: 442.1/444.0 (MH+). $^1$H NMR ($d_6$-DMSO) δ: 10.22 (s, 1H), 9.04 (s, 1H), 7.98 (s, 1H), 7.55 (s, 1H), 7.49-7.46 (m, 1H), 7.26-7.21 (m, 2H), 7.14-7.08 (m, 2H), 7.00 (t, 1H), 6.69 (d, 1H), 3.59 (q, 2H), 3.37 (s, 2H), 2.86 (t, 2H) ppm.

Example 80

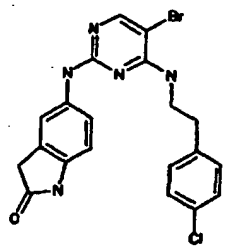
5-[5-Bromo-4-[2-(4-chloro-phenyl)-ethylamino]-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one

A. (5-Bromo-2-chloro-pyrimidin-4-yl)-[2-(4-chloro-phenyl)-ethyl]-amine ($C_{12}H_{10}BrCl_2N_3$).



The title intermediate was isolated as a white solid in an 86% yield. GC/MS: ret. time = 5.36 min; m/z: 345/347/349. $^1$H NMR ($d_6$-DMSO) δ: 8.25 (s, 1H), 7.80-7.76 (t, 1H), 7.38-7.33 (m, 2H), 7.26-7.23 (m, 2H), 3.59 (q, 2H), 2.87 (t, 2H) ppm.

A. 5-[5-Bromo-4-[2-(4-chloro-phenyl)-ethylamino]-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one ($C_{20}H_{17}BrClN_5O$).

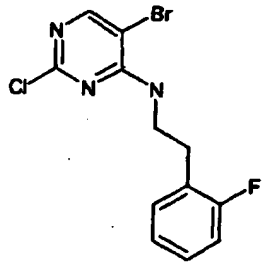


The title compound was isolated as a pink solid in a 39% yield. MS: 458.1/460.0/462.1 (MH+). $^1$H NMR ($d_6$-DMSO) δ: 10.19 (s, 1H), 9.00 (s, 1H), 7.93 (s, 1H), 7.50 (s, 1H), 7.46 (dd, 1H), 7.31-7.29 (m, 2H), 7.19-7.17 (m, 2H), 6.96 (t, 1H), 6.65 (d, 1H), 3.54 (q, 2H), 3.34 (s, 2H), 2.82 (t, 2H) ppm.

Example 81

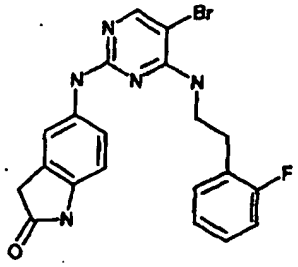
5-[5-Bromo-4-[2-(2-fluoro-phenyl)-ethylamino]-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one

A. (5-Bromo-2-chloro-pyrimidin-4-yl)-[2-(2-fluoro-phenyl)-ethyl]-amine ($C_{12}H_{10}BrClFN_3$).



The title intermediate was isolated as a white solid in an 84% yield. GC/MS: ret. time = 4.67 min; m/z: 329/331/333. $^1$H NMR ($d_6$-DMSO) δ: 8.23 (s, 1H), 7.83 (t, 1H), 7.30-7.23 (m, 2H), 7.18-7.10 (m, 2H), 3.62 (q, 2H), 2.92 (t, 2H) ppm.

B. 5-[5-Bromo-4-[2-(2-fluoro-phenyl)-ethylamino]-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one ($C_{20}H_{17}BrFN_5O$).

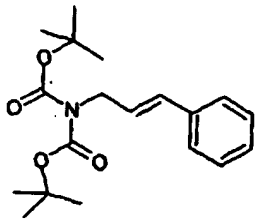


The title compound was isolated as a pink solid in a 19% yield. MS: 442.0/444.0 (MH+). $^1$H NMR ($d_6$-DMSO) δ: 10.17 (s, 1H), 9.00 (s, 1H), 7.93 (s, 1H), 7.52 (s, 1H), 7.42 (dd, 1H), 7.25-7.20 (m, 2H), 7.13-7.06 (m, 2H), 7.01 (t, 1H), 6.64 (d, 1H), 3.58 (q, 2H), 3.32 (s, 2H), 2.88 (t, 2H) ppm.

Example 82

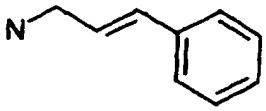
5-[5-Bromo-4-(3-phenyl-allylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one

A. (3-Phenyl-allyl)-carbamic acid di-tert-butyl ester ($C_{18}H_{27}NO_4$).



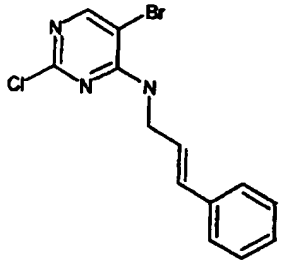
The title intermediate was isolated as a light yellow oil in a 77% yield. GC/MS: ret. time = 4.28 min; m/z: 277 (MH-t-Bu), 234 (MH-BOC), 221 (MH-(t-Bu)$_2$), 177 (MH-BOC-t-Bu), 132 (MH-BOC$_2$), 116 (bp). $^1$H NMR ($d_6$-DMSO) δ: 7.44-7.41 (m, 2H), 7.36-7.31 (m, 2H), 7.28-7.23 (m, 1H), 6.50 (d, 1H), 6.25 (dt, 1H), 4.26 (d, 2H), 1.46 (s, 18H).

B. 3-Phenyl-allylamine ($C_9H_{11}N$).



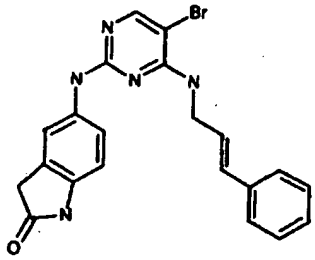
The title intermediate in the crude form as a TFA salt was produced. GC/MS: ret. time = 1.54 min; m/z: 133. $^1$H NMR ($d_6$-DMSO) δ: 7.98 (bs, 2H), 7.42-7.25 (m, 5H), 6.70 (d, 1H), 6.23 (dt, 1H), 3.62-3.57 (m, 2H) ppm.

C. (5-Bromo-2-chloro-pyrimidin-4-yl)-(3-phenyl-allyl)-amine ($C_{13}H_{11}BrClN_3$).



The title intermediate was isolated as a white solid in a 57% yield. GC/MS: ret. time = 5.43 min; m/z: 323/325/327. $^1$H NMR ($d_6$-DMSO) δ: 8.29 (s, 1H), 8.05 (t, 1H), 7.45-7.22 (m, 5H), 6.55-6.50 (m, 1H), 6.34 (dt, 1H), 4.19-4.15 (m, 2H) ppm.

D. 5-[5-Bromo-4-(3-phenyl-allylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one ($C_{21}H_{18}BrN_5O$).

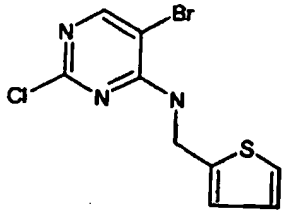


The title compound was isolated as a pink solid in a 42% yield. MS: 436.1/438.0 (MH+). $^1$H NMR ($d_6$-DMSO) δ: 10.20 (s, 1H), 9.07 (s, 1H), 8.01 (s, 1H), 7.61 (s, 1H), 7.48-7.20 (m, 7H), 6.69 (d, 1H), 6.54-6.36 (m, 2H), 4.18 (t, 2H), 3.39 (s, 2H) ppm.

Example 83

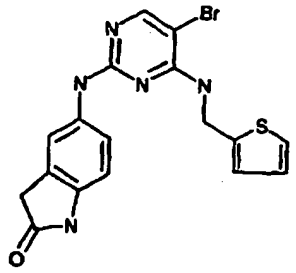
5-[5-Bromo-4-[(thiophen-2-ylmethyl)-amino]-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one

A. (5-Bromo-2-chloro-pyrimidin-4-yl)-thiophen-2-ylmethyl-amine ($C_9H_7BrClN_3S$).



The title intermediate was isolated as a white solid in an 88% yield. GC/MS: ret. time = 4.49 min; m/z: 303/305/307. $^1$H NMR ($d_6$-DMSO) δ: 8.36 (t, 1H), 8.26 (s, 1H), 7.35 (dd, 1H), 7.00-6.99 (m, 1H), 6.93 (dd, 1H), 4.67 (d, 2H) ppm.

B. 5-(5-Bromo-4-[(thiophen-2-ylmethyl)-amino]-pyrimidin-2-ylamino)-1,3-dihydro-indol-2-one ($C_{17}H_{14}BrN_5OS$).

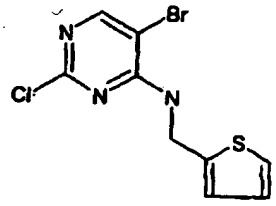


The title compound was isolated as a pink solid in a 29% yield. MS: 416.1/418.1 (MH+). $^1$H NMR ($d_6$-DMSO) δ: 10.15 (s, 1H), 9.05 (s, 1H), 7.97 (s, 1H), 7.57 (t, 1H), 7.51 (s, 1H), 7.39-7.30 (m, 2H), 6.97-6.90 (m, 2H), 6.62 (d, 1H), 4.71 (d, 2H), 3.35 (s, 2H) ppm.

Example 84

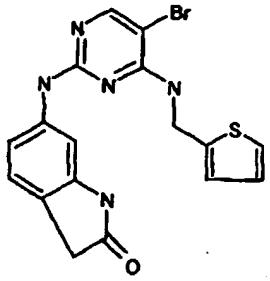
6-(5-Bromo-4-[(thiophen-2-ylmethyl)-amino]-pyrimidin-2-ylamino)-1,3-dihydro-indol-2-one

A. (5-Bromo-2-chloro-pyrimidin-4-yl)-thiophen-2-ylmethyl-amine ($C_9H_7BrClN_3S$).



The title intermediate was isolated as a white solid in an 88% yield. GC/MS: ret. time = 4.49 min; m/z: 303/305/307. $^1$H NMR ($d_6$-DMSO) δ: 8.36 (t, 1H), 8.26 (s, 1H), 7.35 (dd, 1H), 7.00-6.99 (m, 1H), 6.93 (dd, 1H), 4.67 (d, 2H) ppm.

A. 6-(5-Bromo-4-[(thiophen-2-ylmethyl)-amino]-pyrimidin-2-ylamino)-1,3-dihydro-indol-2-one ($C_{17}H_{14}BrN_5OS$).



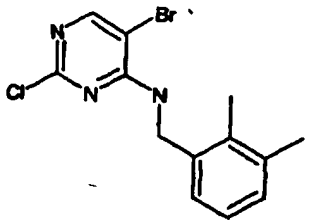
The title compound was isolated as a purple solid in a 27% yield. MS: 416.1/418.1 (MH+). $^1$H NMR ($d_6$-DMSO) δ: 10.32 (s, 1H), 9.22 (s, 1H), 8.00 (s, 1H), 7.59 (t, 1H), 7.36 (d,

1H), 7.29 (dd, 1H), 7.19 (dd, 1H), 7.00-6.97 (m, 2H), 6.91-6.88 (m, 1H), 4.74 (d, 2H), 3.34 (s, 2H) ppm.

Example 85

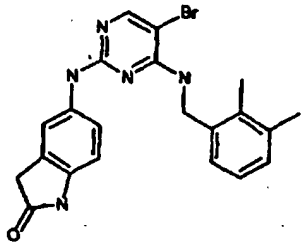
5-[5-Bromo-4-(2,3-dimethyl-benzylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one

A. (5-Bromo-2-chloro-pyrimidin-4-yl)-(2,3-dimethyl-benzyl)-amine ($C_{13}H_{13}BrClN_3$).



The title intermediate was isolated as a white solid in a 72% yield. GC/MS: ret. time = 5.16 min; m/z: 325/327/329. $^1$H NMR ($d_6$-DMSO) δ: 8.25 (s, 1H), 8.13 (t, 1H), 7.03-6.95 (m, 3H), 4.52 (d, 2H), 2.21 (s, 3H), 2.18 (s, 3H) ppm.

B. 5-[5-Bromo-4-(2,3-dimethyl-benzylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one ($C_{21}H_{20}BrN_5O$).

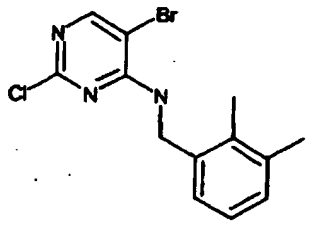


The title compound was isolated as a light pink solid in a 7.7% yield. MS: 438.1/440.1 (MH+). $^1$H NMR ($d_6$-DMSO) δ: 10.12 (s, 1H), 8.97 (s, 1H), 7.98 (s, 1H), 7.32 (s, 2H), 7.16 (d, 1H), 7.02-6.91 (m, 3H), 6.47 (d, 1H), 4.54 (d, 2H), 3.21 (s, 2H), 2.26 (s, 3H), 2.16 (s, 3H) ppm.

Example 86

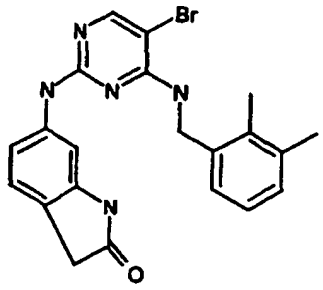
6-[5-Bromo-4-(2,3-dimethyl-benzylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one

A. (5-Bromo-2-chloro-pyrimidin-4-yl)-(2,3-dimethyl-benzyl)-amine ($C_{13}H_{13}BrClN_3$).



The title intermediate was isolated as a white solid in a 72% yield. GC/MS: ret. time = 5.16 min; m/z: 325/327/329. $^1$H NMR ($d_6$-DMSO) δ: 8.25 (s, 1H), 8.13 (t, 1H), 7.03-6.95 (m, 3H), 4.52 (d, 2H), 2.21 (s, 3H), 2.18 (s, 3H) ppm.

B. 6-[5-Bromo-4-(2,3-dimethyl-benzylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one ($C_{21}H_{20}BrN_5O$).

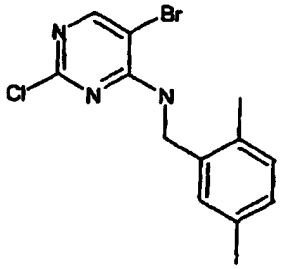


The title compound was isolated as a purple solid in a 21% yield. MS: 438.0/440.2 (MH+). $^1$H NMR ($d_6$-DMSO) δ: 10.24 (s, 1H), 9.12 (s, 1H), 8.01 (s, 1H), 7.26 (t, 1H), 7.18 (s, 1H), 7.07 (dd, 1H), 7.02-6.96 (m, 3H), 6.84 (d, 1H), 4.58 (d, 2H), 3.30 (s, 2H), 2.23 (s, 3H), 2.17 (s, 3H) ppm.

Example 87

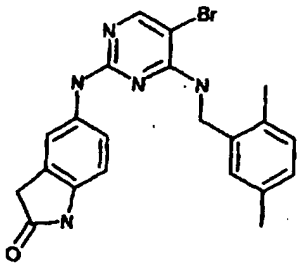
5-[5-Bromo-4-(2,5-dimethyl-benzylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one

A. (5-Bromo-2-chloro-pyrimidin-4-yl)-(2,5-dimethyl-benzyl)-amine ($C_{13}H_{13}BrClN_3$).



The title intermediate was isolated as a white solid in an 84% yield. GC/MS: ret. time = 4.99 min; m/z: 325/327/329. $^1$H NMR ($d_6$-DMSO) δ: 8.24 (s, 1H), 8.16 (t, 1H), 7.02-6.91 (m, 3H), 4.47 (d, 2H), 2.26 (s, 3H), 2.18 (s, 3H) ppm.

B. 5-[5-Bromo-4-(2,5-dimethyl-benzylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one ($C_{21}H_{20}BrN_5O$).

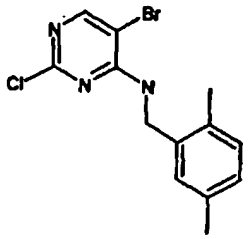


The title compound was isolated as a off white solid in a 9 % yield. MS: 438.1/440.1 (MH+). HPLC: ret. time = 6.48 min. $^1$H NMR ($d_6$-DMSO) δ: 10.12 (s, 1H), 8.99 (s, 1H), 7.98 (s, 1H), 7.35-7.32 (m, 2H), 7.23-7.21 (m, 1H), 7.04-7.02 (m, 1H), 6.91-6.87 (m, 2H), 6.52 (d, 1H), 4.50 (d, 2H), 3.25 (s, 2H), 2.22 (s, 3H), 2.14 (s, 3H) ppm.

Example 88

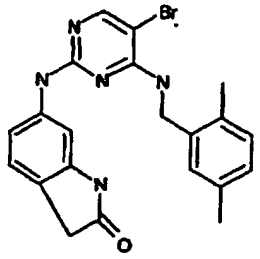
6-[5-Bromo-4-(2,5-dimethyl-benzylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one

A. (5-Bromo-2-chloro-pyrimidin-4-yl)-(2,5-dimethyl-benzyl)-amine ($C_{13}H_{13}BrClN_3$).



The title intermediate was isolated as a white solid in an 84% yield. GC/MS: ret. time = 4.99 min; m/z: 325/327/329. $^1$H NMR ($d_6$-DMSO) δ: 8.24 (s, 1H), 8.16 (t, 1H), 7.02-6.91 (m, 3H), 4.47 (d, 2H), 2.26 (s, 3H), 2.18 (s, 3H) ppm.

B. 6-[5-Bromo-4-(2,5-dimethyl-benzylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one ($C_{21}H_{20}BrN_5O$).

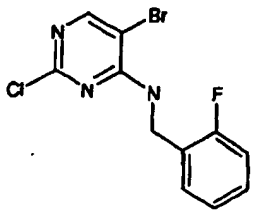


The title compound was isolated as a purple solid in a 4 % yield. MS: 438.1/440.1 (MH+). HPLC: ret. time = 6.86 min. $^1$H NMR ($d_6$-DMSO) δ: 10.26 (s, 1H), 9.13 (s, 1H), 8.01 (s, 1H), 7.28 (t, 1H), 7.20-7.18 (m, 1H), 7.12-7.09 (m, 1H), 7.03-7.01 (m, 1H), 6.95-6.86 (m, 3H), 4.54 (d, 2H), 3.31 (s, 2H), 2.23 (s, 3H), 2.14 (s, 3H) ppm.

Example 89

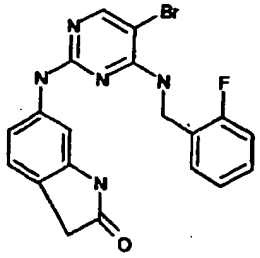
6-[5-Bromo-4-(2-fluoro-benzylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one

A. (5-Bromo-2-chloro-pyrimidin-4-yl)-(2-fluoro-benzyl)-amine ($C_{11}H_8BrClFN_3$).



The title intermediate was isolated as a white solid in a 68% yield. GC/MS: ret. time = 4.75 min; m/z: 315/317/319. $^1$H NMR ($d_6$-DMSO) δ: 8.28-8.25 (m, 2H), 7.31-7.22 (m, 2H), 7.18-7.10 (m, 2H), 4.58 (d, 2H) ppm.

B. 6-[5-Bromo-4-(2-fluoro-benzylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one ($C_{19}H_{15}BrFN_5O$).

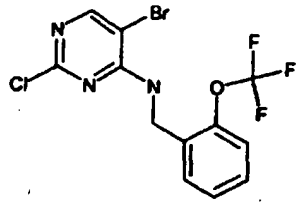


The title compound was isolated as a purple solid in a 6.5% yield. MS: 428.1/430.1 (MH+). $^1$H NMR ($d_6$-DMSO) δ: 10.26 (s, 1H), 9.15 (s, 1H), 8.03 (s, 1H), 7.48 (t, 1H), 7.26-7.09 (m, 6H), 6.87 (d, 1H), 4.65 (d, 2H), 3.31 (s, 2H) ppm.

Example 90

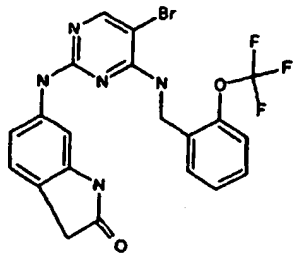
6-[5-Bromo-4-(2-trifluoromethoxy-benzylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one

A. (5-Bromo-2-chloro-pyrimidin-4-yl)-(2-trifluoromethoxy-benzyl)-amine ($C_{12}H_8BrClF_3N_3O$).



The title intermediate was isolated as a white solid in a 66% yield. GC/MS: ret. time = 4.55 min; m/z: 381/383/385. $^1$H NMR ($d_6$-DMSO) δ: 8.28 (m, 2H), 7.40-7.30 (m, 4H), 4.63-4.62 (d, 2H) ppm.

B. 6-[5-Bromo-4-(2-trifluoromethoxy-benzylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one ($C_{20}H_{15}BrF_3N_5O_2$).

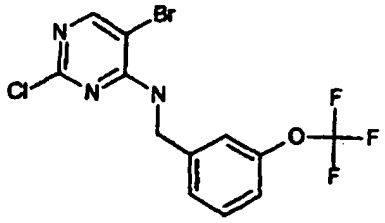


The title compound was isolated as a dark purple solid in a 2% yield. MS: 494.1/496.0 (MH+). $^1$H NMR ($CD_3OD$) δ: 8.00 (s, 1H), 7.41-7.31 (m, 4H), 7.15-7.09 (m, 2H), 7.02-6.99 (m, 1H), 4.81 (s, 2H), 3.46 (s, 2H) ppm.

Example 91

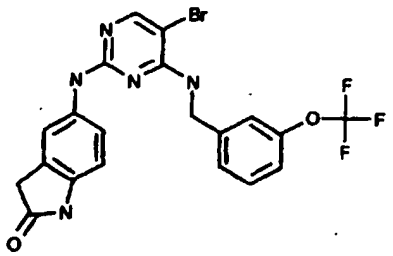
5-[5-Bromo-4-(3-trifluoromethoxy-benzylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one

A. (5-Bromo-2-chloro-pyrimidin-4-yl)-(3-trifluoromethoxy-benzyl)-amine ($C_{12}H_8BrClF_3N_3O$).



The title intermediate was isolated as a colorless oil in a 68% yield. GC/MS: ret. time = 4.75 min; m/z: 381/383/385. $^1$H NMR ($d_6$-DMSO) δ: 8.35 (t, 1H), 8.26 (s, 1H), 7.45-7.41 (m, 1H), 7.31-7.20 (m, 3H), 4.56 (d, 2H) ppm.

B. 5-[5-Bromo-4-(3-trifluoromethoxy-benzylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one ($C_{20}H_{15}BrF_3N_5O_2$).

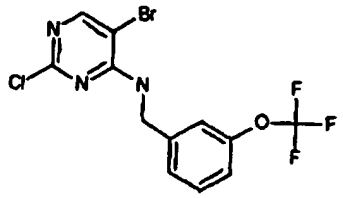


The title compound was isolated as a pink solid in a 38% yield. MS: 494.1/496.1 (MH+). $^1$H NMR ($d_6$-DMSO) δ: 10.16 (s, 1H), 9.02 (s, 1H), 7.98 (s, 1H), 7.61 (t, 1H), 7.44-7.39 (m, 2H), 7.32-7.17 (m, 4H), 6.57 (d, 2H), 4.59 (d, 2H), 3.29 (s, 2H) ppm.

Example 92

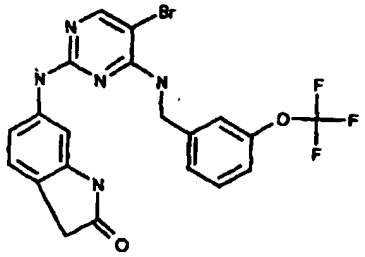
6-[5-Bromo-4-(3-trifluoromethoxy-benzylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one

A. (5-Bromo-2-chloro-pyrimidin-4-yl)-(3-trifluoromethoxy-benzyl)-amine ($C_{12}H_8BrClF_3N_3O$).



The title intermediate was isolated as a colorless oil in a 68% yield. GC/MS: ret. time = 4.75 min; m/z: 381/383/385. $^1$H NMR ($d_6$-DMSO) δ: 8.35 (t, 1H), 8.26 (s, 1H), 7.45-7.41 (m, 1H), 7.31-7.20 (m, 3H), 4.56 (d, 2H) ppm.

B. 6-[5-Bromo-4-(3-trifluoromethoxy-benzylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one ($C_{20}H_{15}BrF_3N_5O_2$).

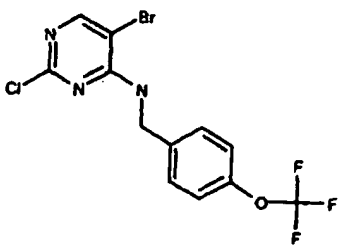


The title compound was isolated as a purple solid in a 4% yield. MS: 494.2/496.2 (MH+). $^1$H NMR ($d_6$-DMSO) δ: 10.32 (s, 1H), 9.17 (s, 1H), 8.01 (s, 1H), 7.65 (t, 1H), 7.42-7.28 (m, 4H), 7.17-7.15 (m, 1H), 7.07 (dd, 1H), 6.92 (d, 1H), 4.62 (d, 2H), 3.31 (s, 2H) ppm.

Example 93

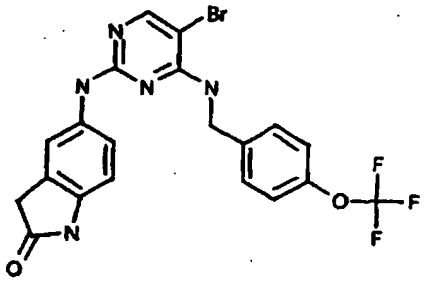
5-[5-Bromo-4-(4-trifluoromethoxy-benzylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one

A. (5-Bromo-2-chloro-pyrimidin-4-yl)-(4-trifluoromethoxy-benzyl)-amine ($C_{12}H_8BrClF_3N_3O$).



The title intermediate was isolated as a colorless oil in a 76% yield. GC/MS: ret. time = 4.88 min; m/z: 381/383/385. $^1$H NMR ($d_6$-DMSO) δ: 8.34 (t, 1H), 8,25 (s, 1H), 7.41-7.37 (m, 2H), 7.30-7.27 (m, 2H), 4.56 (d, 2H) ppm.

B. 5-[5-Bromo-4-(4-trifluoromethoxy-benzylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one ($C_{20}H_{15}BrF_3N_5O_2$).

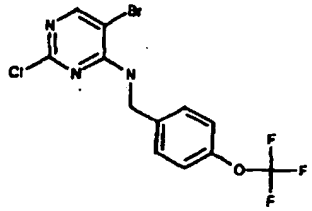


The title compound was isolated as a light gray solid in a 23% yield. MS: 494.0/496.0 (MH+). $^1$H NMR ($d_6$-DMSO) δ: 10.14 (s, 1H), 9.01 (s, 1H), 7.98 (s, 1H), 7.59 (t, 1H), 7.40-7.21 (m, 6H), 6.57 (d, 1H), 4.58 (d, 2H), 3.29 (s, 2H) ppm.

Example 94

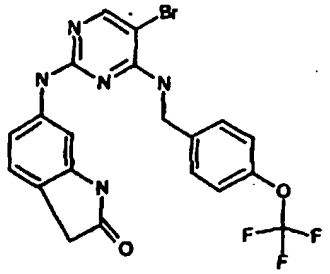
6-[5-Bromo-4-(4-trifluoromethoxy-benzylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one

A. (5-Bromo-2-chloro-pyrimidin-4-yl)-(4-trifluoromethoxy-benzyl)-amine ($C_{12}H_8BrClF_3N_3O$).



The title intermediate was isolated as a colorless oil in a 76% yield. GC/MS: ret. time = 4.88 min; m/z: 381/383/385. $^1$H NMR ($d_6$-DMSO) δ: 8.34 (t, 1H), 8,25 (s, 1H), 7.41-7.37 (m, 2H), 7.30-7.27 (m, 2H), 4.56 (d, 2H) ppm.

B. 6-[5-Bromo-4-(4-trifluoromethoxy-benzylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one ($C_{20}H_{15}BrF_3N_5O_2$).

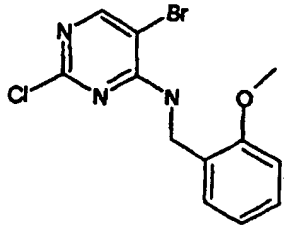


The title compound was isolated as a purple solid in a 25% yield. MS: 494.0/496.0 (MH+). $^1$H NMR ($d_6$-DMSO) δ: 10.31 (s, 1H), 9.16 (s, 1H), 8.01 (s, 1H), 7.61 (t, 1H), 7.42 (d, 2H), 7.28-7.25 (m, 3H), 7.09 (dd, 1H), 6.92 (d, 1H), 4.61 (d, 2H), 3.32 (s, 2H) ppm.

Example 95

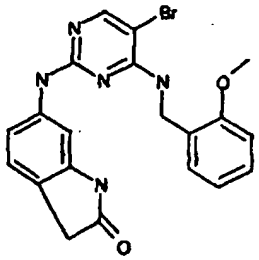
6-[5-Bromo-4-(2-methoxy-benzylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one

A. (5-Bromo-2-chloro-pyrimidin-4-yl)-(2-methoxy-benzyl)-amine ($C_{12}H_{11}BrClN_3O$).



The title intermediate was isolated as a white solid in a 78% yield. GC/MS: ret. time = 5.43 min; m/z: 327/329/331. $^1$H NMR ($d_6$-DMSO) δ: 8.26 (s, 1H), 8.05 (t, 1H), 7.23-7.19 (m, 1H), 7.01-6.96 (m, 2H), 6.88-6.84 (m, 1H), 4.52 (d, 2H), 3.80 (s, 3H) ppm.

B. 6-[5-Bromo-4-(2-methoxy-benzylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one ($C_{20}H_{16}BrN_5O_2$).



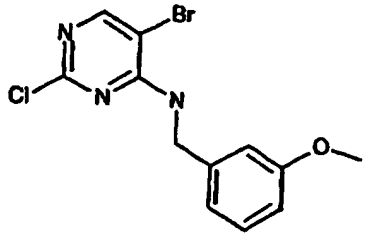
The title compound was isolated as a gray solid in a 12% yield. MS: 440.1/442.1 (MH+). $^1$H NMR ($d_6$-DMSO) δ: 10.31 (s, 1H), 9.17 (s, 1H), 8.00 (s, 1H), 7.54 (t, 1H), 7.29 (s,

1H), 7.20-7.11 (m, 2H), 6.95-6.89 (m, 3H), 6.75-6.73 (m, 1H), 4.56 (d, 2H), 3.63 (s, 3H), 3.32 (s, 2H) ppm.

Example 96

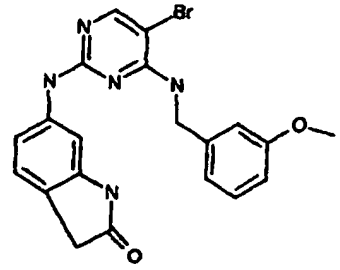
6-[5-Bromo-4-(3-methoxy-benzylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one

A. (5-Bromo-2-chloro-pyrimidin-4-yl)-(3-methoxy-benzyl)-amine ($C_{12}H_{11}BrClN_3O$).



The title intermediate was isolated as a white solid in an 83% yield. GC/MS: ret. time = 5.56 min; m/z: 327/329/331. $^1$H NMR ($d_6$-DMSO) δ: 8.28 (t, 1H), 8.25 (s, 1H), 7.21 (t, 1H), 6.86-6.77 (m, 3H), 4.50 (d, 2H), 3.70 (s, 3H) ppm.

B. 6-[5-Bromo-4-(3-methoxy-benzylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one ($C_{20}H_{18}BrN_5O_2$).

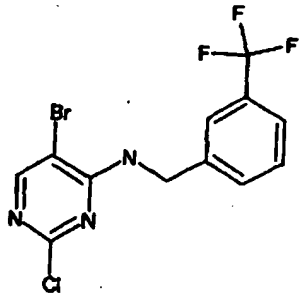


The title compound was isolated as a pink solid in a 5% yield. MS: 440.0/442.0 (MH+). $^1$H NMR ($d_6$-DMSO) δ: 10.23 (s, 1H), 9.11 (s, 1H), 8.02 (s, 1H), 7.21-6.82 (m, 8H), 4.57 (d, 2H), 3.81 (s, 3H), 3.30 (s, 2H) ppm.

Example 97

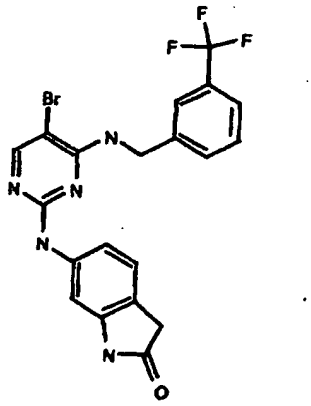
6-[5-Bromo-4-(3-trifluoromethyl-benzylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one

A. (5-Bromo-2-chloro-pyrimidin-4-yl)-(3-trifluoromethyl-benzyl)-amine ($C_{12}H_8BrClF_3N_3$).



The title intermediate was isolated as a white solid in a 78% yield. GC/MS: ret. time = 4.77 min; m/z: 365/367/369. $^1$H NMR ($d_6$-DMSO) δ: 8.38 (t, 1H), 8.26 (s, 1H), 7.67 (s, 1H), 7.59-7.51 (m, 3H), 4.60 (d, 2H) ppm.

B. 6-[5-Bromo-4-(3-trifluoromethyl-benzylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one ($C_{20}H_{15}BrF_3N_5O$).

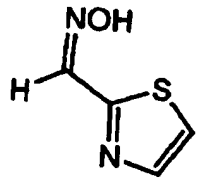


The title compound was isolated as a purple solid in a 10% yield. MS: 478.0/480.0 (MH+). $^1$H NMR ($d_6$-DMSO) δ: 10.33 (s, 1H), 9.18 (s, 1H), 8.01 (s, 1H), 7.71-7.67 (m, 2H), 7.62-6.60 (m, 1H), 7.54-7.48 (m, 2H), 7.29 (d, 1H), 7.05 (dd, 1H), 6.91 (d, 1H), 4.66 (d, 2H), 3.31 (s, 2H) ppm.

Example 98

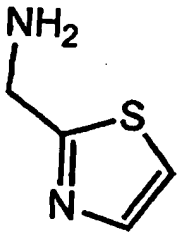
5-{5-Bromo-4-[(thiazol-2-ylmethyl)-amino]-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one

A. Thiazole-2-carbaldehyde oxime ($C_4H_4N_2OS$).



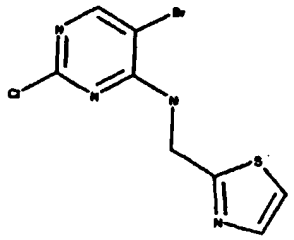
The title intermediate was synthesized following the procedure by Dondoni (Dondoni, A., Fantin, G., Fogagnolo, M., Medici, A., Pedrini, P.; *Synthesis* 1987, 998-1001) and isolated as a light purple solid in a 50% yield. GC/MS: ret. time = 1.55 min and 1.70 min (cis and trans isomers); m/z: 128.

B. C-Thiazol-2-yl-methylamine ($C_4H_6N_2S$).



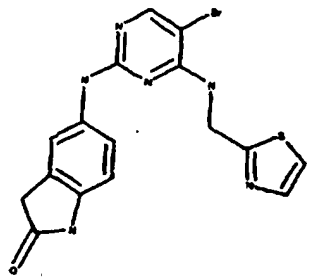
The title intermediate was synthesized following the procedure by Dondoni (Dondoni, A., Merchan, F.L., Merino, P., Rojo, I., Tejero, T.; Synthesis, 1996, 641-646) and isolated as a crude sample in a 21% yield. GC/MS: ret. time = 0.99 min; m/z: 114. $^1$H NMR ($d_6$-DMSO) δ: 7.65 (d, 1H), 7.52 (d, 1H), 3.95 (s, 2H), 3.30 (s, 2H) ppm.

C. (5-Bromo-2-chloro-pyrimidin-4-yl)-thiazol-2-ylmethyl-amine ($C_8H_6BrClN_4S$).



The title intermediate was isolated as a yellow solid in a 45% yield. GC/MS: ret. time = 4.91 min; m/z: 304/306/308. $^1$H NMR ($d_6$-DMSO) δ: 8.55 (t, 1H), 8.33 (s, 1H), 7.71 (d, 1H), 7.60 (d, 1H), 4.81 (d, 2H) ppm.

D. 5-[5-Bromo-4-[(thiazol-2-ylmethyl)-amino]-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one ($C_{16}H_{13}BrN_6OS$).

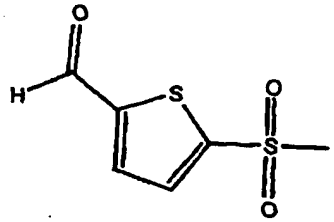


The title compound was isolated as a brown solid in a 43% yield. MS: 417.0/418.9 (MH+). $^1$H NMR ($d_6$-DMSO) δ: 10.15 (s, 1H), 9.10 (s, 1H), 8.02 (s, 1H), 7.82 (sb, 1H), 7.72 (d, 1H), 7.54 (d, 1H), 7.40 (s, 1H), 7.22 (d, 1H), 6.56 (d, 1H), 4.81 (d, 2H), 3.33 (s, 2H) ppm.

Example 99

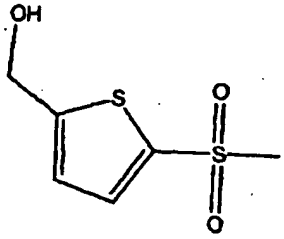
5-[5-Bromo-4-[(5-methanesulfonyl-thiophen-2-ylmethyl)-amino]-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one

A 5-Methanesulfonyl-thiophene-2-carbaldehyde ($C_6H_6O_3S_2$).



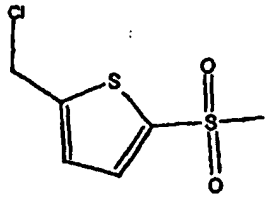
The title intermediate was prepared by adapting the procedure by Archer (Archer, W.J., Cook, R., Taylor, R.; *J. Chem. Soc. Perkin Trans. II*, 1983, 813-819) and isolated as a light yellow solid in a 26% yield. GC/MS: ret. time = 2.96 min; m/z: 190. $^1$H NMR ($d_6$-DMSO) δ: 10.01 (s, 1H), 8.08 (d, 1H), 7.94 (d, 1H), 3.42 (s, 3H) ppm.

B. (5-Methanesulfonyl-thiophen-2-yl)-methanol ($C_6H_8O_3S_2$).



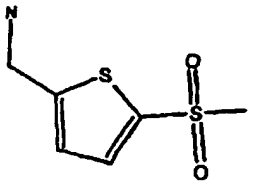
The title intermediate was prepared by adapting the procedure by Lee (Lee, Y. and Silverman, R.B.; *Tetrahedron*, 2001, 53, 5339-5352) and isolated as a yellow oil in a 74% yield. GC/MS: ret. time = 3.55 min; m/z: 192. $^1$H NMR ($d_6$-DMSO) δ: 7.61 (d, 1H), 7.04 (d, 1H), 5.83 (t, 1H), 4.67 (d, 2H), 3.27 (s, 3H) ppm.

C. 2-Chloromethyl-5-methanesulfonyl-thiophene ($C_{13}H_{14}O_5S_3$).



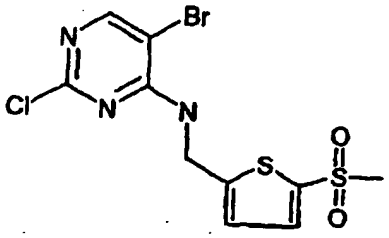
The title intermediate was isolated as a white solid in a 52% yield. GC/MS: ret. time = 3.31 min; m/z: 210/212. $^1$H NMR ($d_6$-DMSO) δ: 7.65 (d, 1H), 7.29 (d, 1H), 5.08 (s, 2H), 3.32 (s, 3H) ppm.

a. C-(5-Methanesulfonyl-thiophen-2-yl)-methylamine ($C_8H_9NO_2S_2$)



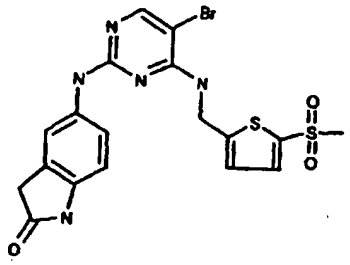
The title intermediate was isolated as a white solid in the TFA salt form in a 75% yield. GC/MS: ret. time = 3.53 min; m/z: 191. $^1$H NMR ($d_6$-DMSO) δ: 8.36 (s, 2H), 7.73 (d, 1H), 7.32 (d, 1H), 4.32 (s, 2H), 3.32 (s, 3H) ppm.

E. (5-Bromo-2-chloro-pyrimidin-4-yl)-(5-methanesulfonyl-thiophen-2-ylmethyl)-amine ($C_{10}H_9BrClN_3O_2S_2$).



The title intermediate was isolated as a light yellow solid in a 74% yield. GC/MS: ret. time = 7.00 min; m/z: 381/383/385. $^1$H NMR ($d_6$-DMSO) δ: 8.49 (t, 1H), 8.31 (s, 1H), 7.62 (d, 1H), 7.14 (d, 1H), 4.72 (d, 2H), 3.27 (s, 3H) ppm.

F. 5-[5-Bromo-4-[(5-methanesulfonyl-thiophen-2-ylmethyl)-amino]-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one ($C_{18}H_{16}BrN_5O_3S_2$).

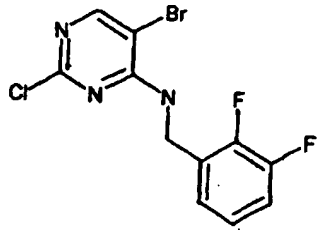


The title compound was isolated as a pink solid in an 18% yield. MS: 494.0/495.9 (MH+). $^1$H NMR ($d_6$-DMSO) δ: 10.18 (s, 1H), 9.11 (s, 1H), 8.01 (s, 1H), 7.74 (t, 1H), 7.61 (d, 1H), 7.47 (s, 1H), 7.34-7.31 (m, 1H), 7.11 (d, 1H), 6.63 (d, 1H), 4.74 (d, 1H), 3.37 (s, 2H), 3.30 (s, 3H) ppm.

Example 100

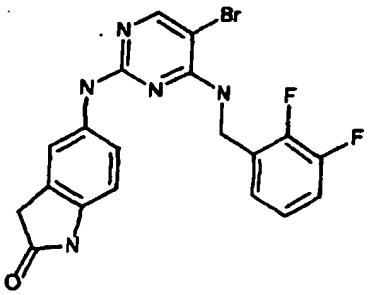
5-[5-Bromo-4-(2,3-difluoro-benzylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one

A. (5-Bromo-2-chloro-pyrimidin-4-yl)-(2,3-difluoro-benzyl)-amine ($C_{11}H_7BrClF_2N_3$).



The title intermediate was isolated as a white solid in a 78% yield. GC/MS: ret. time = 4.77 min; m/z: 333/335/337. $^1$H NMR ($d_6$-DMSO) δ: 8.33 (t, 1H), 8.28 (s, 1H), 7.33-7.26 (m, 1H), 7.16-7.06 (m, 2H), 4.61 (d, 2H) ppm.

B. 5-[5-Bromo-4-(2,3-difluoro-benzylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one ($C_{18}H_{14}BrF_2N_5O$).

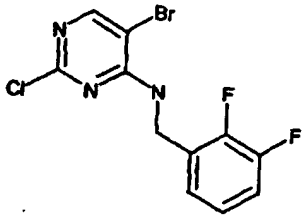


The title compound was isolated as a pink solid in a 33% yield. MS: 446.1/448.0 (MH+). $^1$H NMR ($d_6$-DMSO) δ: 10.16 (s, 1H), 9.05 (s, 1H), 8.00 (s, 1H), 7.58 (t, 1H), 7.32-7.21 (m, 3H), 7.13-7.11 (m, 1H), 7.03-7.01 (m, 1H), 6.54 (d, 1H), 4.65 (d, 2H), 3.28 (s, 2H) ppm.

Example 101

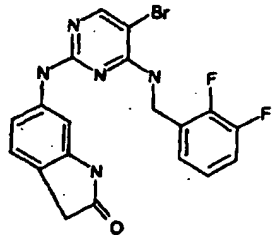
6-[5-Bromo-4-(2,3-difluoro-benzylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one

A. (5-Bromo-2-chloro-pyrimidin-4-yl)-(2,3-difluoro-benzyl)-amine ($C_{11}H_7BrClF_2N_3$).



The title intermediate was isolated as a white solid in a 78% yield. GC/MS: ret. time = 4.77 min; m/z: 333/335/337. $^1$H NMR ($d_6$-DMSO) δ: 8.33 (t, 1H), 8.28 (s, 1H), 7.33-7.26 (m, 1H), 7.16-7.06 (m, 2H), 4.61 (d, 2H) ppm.

B. 6-[5-Bromo-4-(2,3-difluoro-benzylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one ($C_{19}H_{14}BrF_2N_5O$).

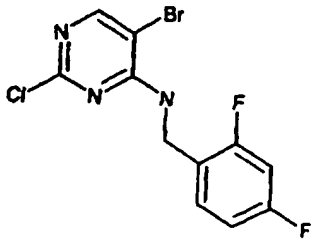


The title compound was isolated as a purple solid in an 8% yield. MS: 446.0/447.9 (MH+). $^1$H NMR ($d_6$-DMSO) δ: 10.28 (s, 1H), 9.18 (s, 1H), 8.04 (s, 1H), 7.57 (t, 1H), 7.28-7.26 (m, 1H), 7.13-7.06 (m, 4H), 6.87 (d, 1H), 4.68 (d, 1H), 3.32 (s, 2H) ppm.

Example 102

5-[5-Bromo-4-(2,4-difluoro-benzylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one

A. (5-Bromo-2-chloro-pyrimidin-4-yl)-(2,4-difluoro-benzyl)-amine ($C_{11}H_7BrClF_2N_3$).



The title compound was isolated as a light purple solid in an 11% yield. MS: 446.2/448.2. $^1$H NMR ($d_6$-DMSO) δ: 10.28 (s, 1H), 9.18 (s, 1H), 8.03 (s, 1H), 7.50 (t, 1H), 7.32, 7.12 (m, 4H), 7.02-6.97 (m, 1H), 6.90 (d, 1H), 4.61 (d, 2H), 3.32 (s, 2H) ppm.

The following compounds were also prepared using the methods described in this application:

6-[5-Chloro-4-(2-trifluoromethyl-benzylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one

5-Chloro-N2-(1-methyl-1H-indol-5-yl)-N4-(2-trifluoromethyl-benzyl)-pyrimidine-2,4-diamine

5-Chloro-$N^2$-(1H-indazol-5-yl)-$N^4$-(2-trifluoromethyl-benzyl)-pyrimidine-2,4-diamine

5-Chloro-$N^2$-(1-methyl-1H-indol-5-yl)-$N^4$-pyridin-2-ylmethyl-pyrimidine-2,4-diamine

6-{5-Chloro-4-[(pyridin-2-ylmethyl)-amino]-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one

5-Chloro-N2-(1H-indazol-6-yl)-N4-(2-trifluoromethyl-benzyl)-pyrimidine-2,4-diamine

5-Chloro-N2-(1H-indazol-6-yl)-N4-pyridin-2-ylmethyl-pyrimidine-2,4-diamine

(5-{5-Bromo-4-[(pyridin-2-ylmethyl)-amino]-pyrimidin-2-ylamino}-indazol-1-yl)-acetic acid tert-butyl ester

(6-{5-Bromo-4-[(pyridin-2-ylmethyl)-amino]-pyrimidin-2-ylamino}-indazol-2-yl)-acetic acid tert-butyl ester

6-{4-[(Pyridin-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one

N2-(1-Methyl-1H-indol-5-yl)-N4-pyridin-2-ylmethyl-5-trifluoromethyl-pyrimidine-2,4-diamine

(6-{5-Bromo-4-[(pyridin-2-ylmethyl)-amino]-pyrimidin-2-ylamino}-indol-1-yl)-acetic acid tert-butyl ester

N4-Pyridin-2-ylmethyl-N2-quinolin-5-yl-5-trifluoromethyl-pyrimidine-2,4-diamine

2-(6-{5-Bromo-4-[(pyridin-2-ylmethyl)-amino]-pyrimidin-2-ylamino}-indol-1-yl)-N-(2-methoxy-ethyl)-acetamide

6-{5-Chloro-4-[(3-methyl-pyridin-2-ylmethyl)-amino]-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one

(6-{5-Bromo-4-[(pyridin-2-ylmethyl)-amino]-pyrimidin-2-ylamino}-indol-1-yl)-acetic acid

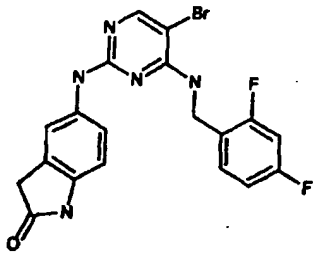
(6-{5-Bromo-4-[(pyridin-2-ylmethyl)-amino]-pyrimidin-2-ylamino}-indazol-1-yl)-acetic acid tert-butyl ester

N2-(1H-Indazol-6-yl)-N4-pyridin-2-ylmethyl-5-trifluoromethyl-pyrimidine-2,4-diamine

(5-{5-Bromo-4-[(pyridin-2-ylmethyl)-amino]-pyrimidin-2-ylamino}-indol-1-yl)-acetic acid tert-butyl ester

The title intermediate was isolated as a white solid in a 78% yield. GC/MS: ret. time = 4.63 min; m/z: 333/335/337. $^1$H NMR ($d_6$-DMSO) δ: 8.28-8.26 (m, 2H), 7.35-7.29 (m, 1H), 7.23-7.17 (m, 1H), 7.04-6.99 (m, 1H), 4.54 (d, 2H) ppm.

B. 5-[5-Bromo-4-(2,4-difluoro-benzylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one ($C_{18}H_{14}BrF_2N_5O$).

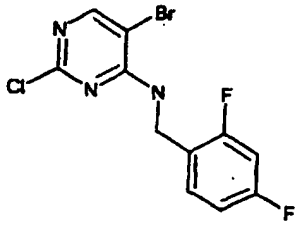


The title compound was isolated as a dark pink solid in a 13% yield. MS: 446.1/448.1 (MH+). $^1$H NMR ($d_6$-DMSO) δ: 10.15 (s, 1H), 9.04 (s, 1H), 8.00 (s, 1H), 7.51 (t, 1H), 7.39 (s, 1H), 7.25-7.20 (m, 3H), 7.03-6.98 (m, 1H), 6.56 (d, 1H), 4.58 (d, 2H), 3.30 (s, 2H) ppm.

Example 103

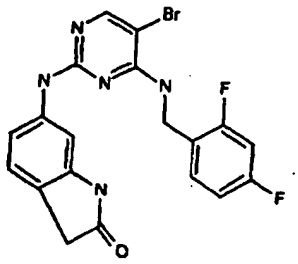
6-[5-Bromo-4-(2,4-difluoro-benzylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one

A. (5-Bromo-2-chloro-pyrimidin-4-yl)-(2,4-difluoro-benzyl)-amine ($C_{11}H_7BrClF_2N_3$).



The title intermediate was isolated as a white solid in a 78% yield. GC/MS: ret. time = 4.63 min; m/z: 333/335/337. $^1$H NMR ($d_6$-DMSO) δ: 8.28-8.26 (m, 2H), 7.35-7.29 (m, 1H), 7.23-7.17 (m, 1H), 7.04-6.99 (m, 1H), 4.54 (d, 2H) ppm.

B. 6-[5-Bromo-4-(2,4-difluoro-benzylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one (($C_{18}H_{14}BrF_2N_5O$).



(6-{5-Bromo-4-[(pyridin-2-ylmethyl)-amino]-pyrimidin-2-ylamino}-indazol-1-yl)-acetic acid

(5-{5-Bromo-4-[(pyridin-2-ylmethyl)-amino]-pyrimidin-2-ylamino}-indol-1-yl)-acetic acid

(5-{5-Bromo-4-[(pyridin-2-ylmethyl)-amino]-pyrimidin-2-ylamino}-indazol-1-yl)-acetic acid

5-{5-Chloro-4-[(3-methyl-pyridin-2-ylmethyl)-amino]-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one

5-[5-Chloro-4-(3-methanesulfonyl-benzylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one

6-[5-Chloro-4-(3-methyl-benzylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one

5-[5-Chloro-4-(2-fluoro-benzylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one

6-[5-Chloro-4-(2-fluoro-benzylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one

5-[5-Bromo-4-(2-methoxy-ethylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one

5-[5-Chloro-4-(3-methyl-benzylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one

6-[5-Chloro-4-[(4-methyl-pyridin-2-ylmethyl)-amino]-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one

5-(4-Benzylamino-5-chloro-pyrimidin-2-ylamino)-1,3-dihydro-indol-2-one

5-Bromo-N2-(1H-indol-5-yl)-N4-pyridin-2-ylmethyl-pyrimidine-2,4-diamine

5-Bromo-N2-(1H-indol-5-yl)-N4-(2-pyridin-2-yl-ethyl)-pyrimidine-2,4-diamine

5-Bromo-N2-(1H-indol-4-yl)-N4-(2-pyridin-2-yl-ethyl)-pyrimidine-2,4-diamine

5-Bromo-N2-(1H-indazol-5-yl)-N4-(2-pyridin-2-yl-ethyl)-pyrimidine-2,4-diamine

5-Bromo-N2-(1H-indazol-6-yl)-N4-(2-pyridin-2-yl-ethyl)-pyrimidine-2,4-diamine

5-Bromo-N2-(1H-indol-4-yl)-N4-pyridin-2-ylmethyl-pyrimidine-2,4-diamine

5-Bromo-N2-(1H-indazol-5-yl)-N4-pyridin-2-ylmethyl-pyrimidine-2,4-diamine

N2-(1H-Indol-5-yl)-N4-pyridin-2-ylmethyl-pyrimidine-2,4-diamine

N2-(1H-Indazol-6-yl)-N4-pyridin-2-ylmethyl-pyrimidine-2,4-diamine

N2-(1H-Indol-5-yl)-N4-(2-pyridin-2-yl-ethyl)-pyrimidine-2,4-diamine

N2-(1H-Indazol-5-yl)-N4-pyridin-2-ylmethyl-pyrimidine-2,4-diamine

N2-(1H-Indazol-5-yl)-N4-(2-pyridin-2-yl-ethyl)-pyrimidine-2,4-diamine

N2-(1H-Indazol-6-yl)-N4-(2-pyridin-2-yl-ethyl)-pyrimidine-2,4-diamine

5-{5-Bromo-4-[(pyridin-2-ylmethyl)-amino]-pyrimidin-2-ylamino}-1,3-dihydro-benzoimidazol-2-one

5-[5-Bromo-4-(2-pyridin-2-yl-ethylamino)-pyrimidin-2-ylamino]-1,3-dihydro-benzoimidazol-2-one

5-[4-[(Pyridin-2-ylmethyl)-amino]-pyrimidin-2-ylamino}-1,3-dihydro-benzoimidazol-2-one

5-[4-(2-Pyridin-2-yl-ethylamino)-pyrimidin-2-ylamino]-1,3-dihydro-benzoimidazol-2-one

5-Bromo-N2-(1H-indazol-6-yl)-N4-pyridin-2-ylmethyl-pyrimidine-2,4-diamine

5-[5-Bromo-4-[(pyridin-2-ylmethyl)-amino]-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one

5-[5-Bromo-4-(2-pyridin-2-yl-ethylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one

5-[4-(2-Pyridin-2-yl-ethylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one

5-Bromo-N2-(2-methyl-1H-indol-5-yl)-N4-(2-pyridin-2-yl-ethyl)-pyrimidine-2,4-diamine

N2-(2-Methyl-1H-indol-5-yl)-N4-pyridin-2-ylmethyl-pyrimidine-2,4-diamine

N2-(1H-Indol-6-yl)-N4-pyridin-2-ylmethyl-pyrimidine-2,4-diamine

5-Bromo-N2-(2-methyl-1H-indol-5-yl)-N4-pyridin-2-ylmethyl-pyrimidine-2,4-diamine

5-Bromo-N2-(1H-indol-6-yl)-N4-pyridin-2-ylmethyl-pyrimidine-2,4-diamine

5-Bromo-N2-(1H-indol-6-yl)-N4-(2-pyridin-2-yl-ethyl)-pyrimidine2,4-diamine

N2-(1H-Benzoimidazol-5-yl)-5-bromo-N4-pyridin-2-ylmethyl-pyrimidine-2,4-diamine

N2-(1H-Benzoimidazol-5-yl)-5-bromo-N4-(2-pyridin-2-yl-ethyl)-pyrimidine-2,4-diamine

3-[5-Bromo-4-(2-pyridin-2-yl-ethylamino)-pyrimidin-2-yl]-3H-benzoimidazol-5-ylamine

N2-(1H-Benzoimidazol-5-yl)-N4-pyridin-2-ylmethyl-pyrimidine-2,4-diamine

5-Bromo-N2-(2-methyl-1H-benzoimidazol-5-yl)-N4-pyridin-2-ylmethyl-pyrimidine-2,4-diamine

N2-(2-Methyl-1H-benzoimidazol-5-yl)-N4-pyridin-2-ylmethyl-pyrimidine-2,4-diamine

5-Bromo-N2-(2-methyl-1H-benzoimidazol-5-yl)-N4-(2-pyridin-2-yl-ethyl)-pyrimidine-2,4-diamine

5-Bromo-N2-(2,3-dihydro-1H-indol-5-yl)-N4-(2-pyridin-2-yl-ethyl)-pyrimidine-2,4-diamine

N2-(2,3-Dihydro-1H-indol-5-yl)-N4-pyridin-2-ylmethyl-pyrimidine-2,4-diamine

5-Bromo-N2-(1-methyl-1H-indol-5-yl)-N4-(2-pyridin-2-yl-ethyl)-pyrimidine-2,4-diamine

N2-(1-Methyl-1H-indol-5-yl)-N4-pyridin-2-ylmethyl-pyrimidine-2,4-diamine

5-Bromo-N2-(2,3-dihydro-1H-indol-5-yl)-N4-pyridin-2-ylmethyl-pyrimidine-2,4-diamine

5-Bromo-N2-(1-methyl-1H-indol-5-yl)-N4-pyridin-2-ylmethyl-pyrimidine-2,4-diamine

5-Fluoro-N4-pyridin-2-ylmethyl-N2-quinolin-6-yl-pyrimidine-2,4-diamine

5-Bromo-N4-pyridin-2-ylmethyl-N2-quinolin-6-yl-pyrimidine-2,4-diamine

5-Bromo-N2-(1H-indol-7-yl)-N4-(2-pyridin-2-yl-ethyl)-pyrimidine-2,4-diamine

5-Bromo-N2-(1H-indol-7-yl)-N4-pyridin-2-ylmethyl-pyrimidine-2,4-diamine

5-Bromo-N2-(1H-indazol-4-yl)-N4-pyridin-2-ylmethyl-pyrimidine-2,4-diamine

6-[5-Bromo-4-[(pyridin-2-ylmethyl)-amino]-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one

5-Bromo-N2-(1H-indazol-4-yl)-N4-(2-pyridin-2-yl-ethyl)-pyrimidine-2,4-diamine

5-Bromo-N4-(2-pyridin-2-yl-ethyl)-N2-quinolin-6-yl-pyrimidine-2,4-diamine

5-Bromo-N4-pyridin-2-ylmethyl-N2-quinolin-5-yl-pyrimidine-2,4-diamine

5-Bromo-N4-(2-pyridin-2-yl-ethyl)-N2-quinolin-5-yl-pyrimidine-2,4-diamine

6-[5-Bromo-4-(2-pyridin-2-yl-ethylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one

5-Bromo-N4-pyridin-2-ylmethyl-N2-quinolin-8-yl-pyrimidine-2,4-diamine

5-Bromo-N4-(2-pyridin-2-yl-ethyl)-N2-quinolin-8-yl-pyrimidine-2,4-diamine

5-{5-Bromo-4-[(pyridin-2-ylmethyl)-amino]-pyrimidin-2-ylamino}-1H-indole-2-carboxylic acid ethyl ester

6-[5-Bromo-4-(2-trifluoromethyl-benzylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one

5-Bromo-N2-(1H-indazol-5-yl)-N4-(2-trifluoromethyl-benzyl)-pyrimidine-2,4-diamine

5-Bromo-N2-(1H-indazol-6-yl)-N4-(2-trifluoromethyl-benzyl)-pyrimidine-2,4-diamine

5-Bromo-N2-(1-methyl-1H-indol-5-yl)-N4-(2-trifluoromethyl-benzyl)-pyrimidine-2,4-diamine

5-Bromo-N2-(1H-indazol-7-yl)-N4-pyridin-2-ylmethyl-pyrimidine-2,4-diamine

5-Bromo-N2-(1H-indazol-4-yl)-N4-(2-trifluoromethyl-benzyl)-pyrimidine-2,4-diamine

6-{5-Bromo-4-[(pyridin-2-ylmethyl)-amino]-pyrimidin-2-ylamino}-3H-isobenzofuran-1-one

N2-Benzothiazol-6-yl-5-bromo-N4-pyridin-2-ylmethyl-pyrimidine-2,4-diamine

5-{5-Bromo-4-[(pyridin-2-ylmethyl)-amino]-pyrimidin-2-ylamino}-2-methyl-1H-indole-3-carbonitrile

5-Bromo-N4-pyridin-2-ylmethyl-N2-(1-pyridin-2-ylmethyl-1H-indazol-5-yl)-pyrimidine-2,4-diamine

N2-(1-Benzyl-1H-indol-5-yl)-5-bromo-N4-pyridin-2-ylmethyl-pyrimidine-2,4-diamine

5-Bromo-N4-pyridin-2-ylmethyl-N2-(1-pyridin-2-ylmethyl-1H-indol-5-yl)-pyrimidine-2,4-diamine

N2-(1-Benzyl-1H-indazol-5-yl)-5-bromo-N4-pyridin-2-ylmethyl-pyrimidine-2,4-diamine

5-Bromo-N2-(1-methyl-1H-indazol-5-yl)-N4-pyridin-2-ylmethyl-pyrimidine-2,4-diamine

5-Bromo-N4-(4-methyl-cyclohexyl)-N2-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine

5-Bromo-N4-(4-methyl-cyclohexyl)-N2-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine

5-Bromo-N4-cyclohexylmethyl-N2-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine

1-{5-Fluoro-4-[(pyridin-2-ylmethyl)-amino]-pyrimidin-2-yl}-3- (1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-ylamine

1-{5-Chloro-4-[(pyridin-2-ylmethyl)-amino]-pyrimidin-2-yl}-3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-ylamine

5-Fluoro-N2-(1H-indazol-5-yl)-N4-pyridin-2-ylmethyl-pyrimidine-2,4-diamine

5-{5-Fluoro-4-[(pyridin-2-ylmethyl)-amino]-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one

5-Chloro-N2-(1H-indazol-5-yl)-N4-pyridin-2-ylmethyl-pyrimidine-2,4-diamine

5-{5-Chloro-4-[(pyridin-2-ylmethyl)-amino]-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one

5-Fluoro-N4-(2-pyridin-2-yl-ethyl)-N2-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine

5-Chloro-N4-(2-pyridin-2-yl-ethyl)-N2-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine

5-Fluoro-N2-(1H-indazol-5-yl)-N4-(2-pyridin-2-yl-ethyl)-pyrimidine-2,4-diamine

5-[5-Fluoro-4-(2-pyridin-2-yl-ethylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one

5-Chloro-N2-(1H-indazol-5-yl)-N4-(2-pyridin-2-yl-ethyl)-pyrimidine-2,4-diamine

5-[5-Chloro-4-(2-pyridin-2-yl-ethylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one

5-{4-[(Pyridin-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one

5-{5-Methoxy-4-[(pyridin-2-ylmethyl)-amino]-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one

5-[5-Methoxy-4-(2-pyridin-2-yl-ethylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one

5-[5-Methoxy-4-(2-trifluoromethyl-benzylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one

5-{5-Bromo-4-[(cyclohex-1-enylmethyl)-amino]-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one

5-[5-Bromo-4-(methyl-pyridin-2-ylmethyl-amino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one

5-[5-Bromo-4-(4-methyl-cyclohexylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one

5-[5-Bromo-4-(4-methyl-cyclohexylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one

5-[5-Bromo-4-(cyclohexylmethyl-amino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one

5-[5-Chloro-4-(2-trifluoromethyl-benzylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one

2-(2-Oxo-2,3-dihydro-1H-indol-5-ylamino)-4-[(pyridin-2-ylmethyl)-amino]-pyrimidine-5-carbonitrile

5-{5-Methyl-4-[(pyridin-2-ylmethyl)-amino]-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one

N2-(1H-Indazol-5-yl)-5-methyl-N4-pyridin-2-ylmethyl-pyrimidine-2,4-diamine

5-Fluoro-N4-pyridin-2-ylmethyl-N2-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine

5-Chloro-N4-pyridin-2-ylmethyl-N2-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine

2-(2-Oxo-2,3-dihydro-1H-indol-5-ylamino)-4-(2-trifluoromethyl-benzylamino)-pyrimidine-5-carbonitrile

5-{4-[Methyl-(2-pyridin-2-yl-ethyl)-amino]-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one

5-Bromo-N4-cyclohex-1-enylmethyl-N2-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine

N2-(1H-Indazol-5-yl)-N4-pyridin-2-ylmethyl-5-trifluoromethyl-pyrimidine-2,4-diamine

5-[5-Trifluoromethyl-4-(2-trifluoromethyl-benzylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one

6-{2-[(Pyridin-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-4-ylamino}-1,3-dihydro-indol-2-one

5-[5-Bromo-4-(piperidin-4-ylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one

5-[4-(1-Acetyl-piperidin-4-ylamino)-5-bromo-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one

2-(2-Oxo-2,3-dihydro-1H-indol-6-ylamino)-4-[(pyridin-2-ylmethyl)-amino]-pyrimidine-5-carbonitrile

5-{4-[(3-Methyl-pyridin-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one

6-{4-[(3-Methyl-pyridin-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one

4-[5-Bromo-2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-pyrimidin-4-ylamino]-piperidine-1-carboxylic acid tert-butyl ester

5-[5-Bromo-4-(1-methanesulfonyl-piperidin-4-ylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one

5-[5-Bromo-4-(piperidin-3-ylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one

4-[5-Bromo-2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-pyrimidin-4-ylamino]-piperidine-1-carboxylic acid ethylamide

3-[5-Bromo-2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-pyrimidin-4-ylamino]-piperidine-1-carboxylic acid ethylamide

5-[4-(1-Benzoyl-piperidin-4-ylamino)-5-bromo-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one

6-[4-(3-Methanesulfonyl-benzylamino)-5-methoxy-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one

6-[4-(3-Methanesulfonyl-benzylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one

6-[4-(3-Methanesulfonyl-benzylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one

5-[4-(1-Benzenesulfonyl-piperidin-4-ylamino)-5-bromo-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one

5-[4-(3-Methanesulfonyl-benzylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one

6-{5-Chloro-4-[(piperidin-3-ylmethyl)-amino]-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one

6-{5-Chloro-4-[(1-methanesulfonyl-piperidin-3-ylmethyl)-amino]-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one

6-{5-Bromo-4-[(piperidin-3-ylmethyl)-amino]-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one

6-{5-Bromo-4-[(1-methanesulfonyl-piperidin-3-ylmethyl)-amino]-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one

5-[5-Fluoro-4-(3-methanesulfonyl-benzylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one

5-{5-Bromo-4-[(1-hydroxy-cyclohexylmethyl)-amino]-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one.

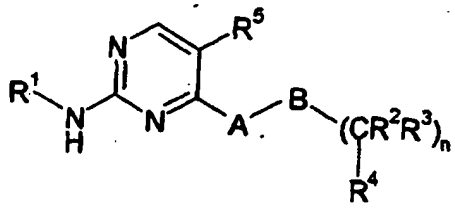
* * *

The present invention is not to be limited in scope by the specific embodiments described herein. Indeed, various modifications of the invention in addition to those described herein will become apparent to those skilled in the art from the foregoing description and the accompanying figures. Such modifications are intended to fall within the scope of the appended claims.

All patents, applications, publications, test methods, literature, and other materials cited herein are hereby incorporated herein by reference in their entireties.

## CLAIMS

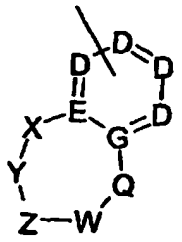
1. A compound of the formula 1



1

or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof,

wherein $R^1$ has the following formula 2



2

wherein each D is independently selected from the group consisting of $CR^8$ and N, with the proviso that $R^1$ is linked to NH group through a ring carbon atom;

wherein E and G are independently selected from the group consisting of N and C;

wherein X, W and Q are independently selected from the group consisting of N, O, S, $SO_2$, CO, $NR^3$, $CR^2$ and $CR^2R^3$;

wherein Y and Z are independently present or absent, if present Y and Z are selected from the group consisting of N, O, S, $SO_2$, CO, $NR^3$, $CR^2$ and $CR^2R^3$;

wherein A is present or absent, if present A is selected from the group consisting of O, S and NH and wherein B is present or absent, if present B is selected from the group consisting of CO, $SO_2$, and $NR^6$, with the proviso that when A is O or S that B is absent;

wherein n is an integer from 1 to 3;

wherein each $R^2$ is independently selected from the group consisting of H, $C_1$-$C_6$ alkyl, $C_3$-$C_7$ cycloalkyl, $C_4$-$C_7$ heterocycloalkyl, $OC_1$-$C_6$ alkyl, $OC_3$-$C_7$ cycloalkyl, $OC_4$-$C_7$ heterocycloalkyl, $NH_2$, $NHR^6$, $NR^6R^7$, $SR^6$, $SOR^6$, $SO_2R^6$, $CO_2R^6$, $CONH_2$, $CONHR^6$, $CONR^6R^7$, $SO_2NH_2$, $SO_2NHR^6$, $SO_2NR^6R^7$, $NHCOR^6$, $NR^6CONR^6$, $NHCONHR^6$, $NR^6CONHR^6$, $NHCONR^6R^7$, $NR^6CONR^6R^7$, $NHSO_2R^6$, $NR^6SO_2R^6$, with the proviso that O, N or S atom of the foregoing substituents may not be bound to a carbon atom bound to another heteroatom, said alkyl, cycloalkyl, heterocycloalkyl moieties of the foregoing groups are optionally substituted by 1 to 3 substituents independently selected from the group consisting of H, halo, $C_1$-$C_6$ alkyl, CN, $NH_2$,

$NHR^{10}$, $N(R^{10})_2$, $OR^{10}$, $C_1$-$C_6$ alkyl, $C_3$-$C_7$ cycloalkyl, $C_4$-$C_7$ heterocycloalkyl, $CO_2R^{11}$, $CONH_2$, $CONHR^{11}$, and $CONR^{11}R^{12}$;

wherein each $R^3$ is independently selected from the group consisting of H, $C_1$-$C_6$ alkyl, $C_3$-$C_7$ cycloalkyl, $C_4$-$C_7$ heterocycloalkyl, $CO_2R^8$, $CONH_2$, $CONHR^6$, $CONR^6R^7$ or $R^2$ and $R^3$ taken together with the carbon atom they are linked to can form a 3-7 membered cycloalkyl ring or 4-7 membered heterocycloalkyl ring, wherein each methylene group present in said 3-7 membered cycloalkyl ring and said 4-7 membered heterocycloalkyl ring may be optionally replaced by a C=O group, said alkyl, cycloalkyl, heterocycloalkyl moieties of the foregoing groups are optionally substituted by 1 to 3 substituents independently selected from the group consisting of H, halo, $C_1$-$C_6$ alkyl, CN, $NH_2$, $NHR^{10}$, $N(R^{10})_2$, $OR^{10}$, $C_1$-$C_6$ alkyl, $C_3$-$C_7$ cycloalkyl, $C_4$-$C_7$ heterocycloalkyl, $CO_2R^{11}$, $CONH_2$, $CONHR^{11}$, and $CONR^{11}R^{12}$;

wherein $R^4$ is selected from the group consisting of H, $C_1$-$C_6$ alkyl, $C_3$-$C_7$ cycloalkyl, $C_4$-$C_7$ heterocycloalkyl, $C_6$-$C_{10}$ aryl, and 5-10 membered heteroaryl, the alkyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl moieties of the foregoing groups are optionally substituted by 1 to 3 subsitutents independently selected from the group consisting of H, halo, OH, $NO_2$, $C_1$-$C_6$ alkyl, $C(R^6)=CR^6R^7$, $C\equiv CR^6$, $C_3$-$C_7$ cycloalkyl, $C_4$-$C_7$ heterocycloalkyl, $OC_1$-$C_6$ alkyl, $OC_3$-$C_7$ cycloalkyl, $OC_4$-$C_7$ heterocycloalkyl, C=N-OH, C=N-O($C_1$-$C_6$ alkyl), $NH_2$, $NHR^6$, $NR^6R^7$, $SR^6$, $SOR^6$, $SO_2R^6$, $CO_2R^6$, $CONH_2$, $CONHR^6$, $CONR^6R^7$, $SO_2NH_2$, $SO_2NHR^6$, $SO_2NR^6R^7$, $NHCOR^6$, $NR^6CONR^6$, $NHCONHR^6$, $NR^6CONHR^6$, $NHCONR^6R^7$, $NR^6CONR^6R^7$, $NHSO_2R^6$, $NR^6SO_2R^6$, with the proviso that O, N or S atom of the foregoing substituents may not be bound to a carbon atom bound to another heteroatom;

wherein $R^5$ is selected from the group consisting of H, Br, Cl, CN, $CF_3$, $CH_2F$, $CHF_2$, $SO_2CH_3$, $CONH_2$, cyclopropyl, cyclobutyl, $C_6H_5$, $CONHR^6$, $CONR^6R^7$, $CO_2R^6$, $C(R^9)=C(R^9)_2$, and $C\equiv CR^9$;

wherein each $R^6$ is independently selected from the group consisting of H, $C_1$-$C_6$ alkyl, $C_3$-$C_7$ cycloalkyl, $C_4$-$C_7$ heterocycloalkyl, $C_6$-$C_{10}$ aryl, and 5-10 membered heteroaryl, said alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl moieties of the foregoing groups are optionally substituted by 1 to 3 substituents independently selected from the group consisting of H, halo, $C_1$-$C_6$ alkyl, CN, $NH_2$, $NHR^{10}$, $N(R^{10})_2$, $OR^{10}$, $C_1$-$C_6$ alkyl, $C_3$-$C_7$ cycloalkyl, $C_4$-$C_7$ heterocycloalkyl, $CO_2R^{11}$, $CONH_2$, $CONHR^{11}$, and $CONR^{11}R^{12}$;

wherein each $R^7$ is independently selected from the group consisting of H, $C_1$-$C_6$ alkyl, $C_3$-$C_7$ cycloalkyl, $C_4$-$C_7$ heterocycloalkyl, $C_6$-$C_{10}$ aryl, and 5-10 membered heteroaryl, said alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl moieties of the foregoing groups are optionally substituted by 1 to 3 substituents independently selected from the group consisting of H, halo, $C_1$-$C_6$ alkyl, CN, $NH_2$, $NHR^{10}$, $N(R^{10})_2$, $OR^{10}$, $C_1$-$C_6$ alkyl, $C_3$-$C_7$ cycloalkyl, $C_4$-$C_7$ heterocycloalkyl, $CO_2R^{11}$, $CONH_2$, $CONHR^{11}$, and $CONR^{11}R^{12}$;

wherein each $R^8$ is independently selected from the group consisting of H, halo, cyano, $C_1$-$C_6$ alkyl, $C_3$-$C_7$ cycloalkyl, $C_4$-$C_7$ heterocycloalkyl, $OC_1$-$C_6$ alkyl, $OC_3$-$C_7$ cycloalkyl, $OC_4$-$C_7$ heterocycloalkyl, $NH_2$, $NHR^6$, $NR^6R^7$, $SR^6$, $SOR^6$, $SO_2R^6$, $CO_2R^6$, $CONH_2$, $CONHR^6$, $CONR^6R^7$, $SO_2NH_2$, $SO_2NHR^6$, $SO_2NR^6R^7$, $NHCOR^6$, $NR^6CONR^6$, $NHCONHR^6$, $NR^6CONHR^6$, $NHCONR^6R^7$, $NR^6CONR^6R^7$, $NHSO_2R^6$, $NR^6SO_2R^6$, said alkyl, cycloalkyl, and heterocycloalkyl moieties of the foregoing groups are optionally substituted by 1 to 3 substituents independently selected from the group consisting of H, halo, $C_1$-$C_6$ alkyl, CN, $NH_2$, $NHR^3$, $N(R^3)_2$, $OR^3$, $C_1$-$C_6$ alkyl, $C_3$-$C_7$ cycloalkyl, $C_4$-$C_7$ heterocycloalkyl, $CO_2R^6$, $CONH_2$, $CONHR^6$, and $CONR^6R^7$; and

wherein each $R^9$ is independently selected from the group consisting of H, $CF_3$, and $C_1$-$C_6$ alkyl, said $C_1$-$C_6$ alkyl is optionally substituted by 1 to 6 halo atoms;

wherein each $R^{10}$ is independently selected from the group consisting of H, $C_1$-$C_6$ alkyl, $C_3$-$C_7$ cycloalkyl, $C_4$-$C_7$ heterocycloalkyl, $CO_2R^{11}$, $CONH_2$, $CONHR^{11}$, $CONR^{11}R^{12}$, $SOR^{11}$, $SO_2R^{11}$, $SO_2NH_2$, $SO_2NHR^{11}$, $SO_2NR^{11}R^{12}$; said alkyl, cycloalkyl, heterocycloalkyl moieties of the foregoing groups are optionally substituted by 1 to 3 substituents independently selected from the group consisting of H, halo, $C_1$-$C_6$ alkyl, CN, $NH_2$, $NHR^{13}$, $N(R^{13})_2$, $OR^{13}$, $C_1$-$C_6$ alkyl, $C_3$-$C_7$ cycloalkyl, $C_4$-$C_7$ heterocycloalkyl, $CO_2R^{14}$, $CONH_2$, $CONHR^{14}$, and $CONR^{14}R^{15}$;

wherein each $R^{11}$ is independently selected from the group consisting of H, $C_1$-$C_6$ alkyl, $C_3$-$C_7$ cycloalkyl, $C_4$-$C_7$ heterocycloalkyl, $C_6$-$C_{10}$ aryl, $C_5$-$C_{10}$ membered heteroaryl; said alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl moieties of the foregoing groups are optionally substituted by 1 to 3 substituents independently selected from the group consisting of H, halo, $C_1$-$C_6$ alkyl, CN, $NH_2$, $NHR^{13}$, $N(R^{13})_2$, $OR^{13}$, $C_1$-$C_6$ alkyl, $C_3$-$C_7$ cycloalkyl, $C_4$-$C_7$ heterocycloalkyl, $CO_2R^{14}$, $CONH_2$, $CONHR^{14}$, and $CONR^{14}R^{15}$;

wherein each $R^{12}$ is independently selected from the group consisting of H, $C_1$-$C_6$ alkyl, $C_3$-$C_7$ cycloalkyl, $C_4$-$C_7$ heterocycloalkyl, $C_6$-$C_{10}$ aryl, $C_5$-$C_{10}$ membered heteroaryl; said alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl moieties of the foregoing groups are optionally substituted by 1 to 3 substituents independently selected from the group consisting of H, halo, $C_1$-$C_6$ alkyl, CN, $NH_2$, $NHR^{13}$, $N(R^{13})_2$, $OR^{13}$, $C_1$-$C_6$ alkyl, $C_3$-$C_7$ cycloalkyl, $C_4$-$C_7$ heterocycloalkyl, $CO_2R^{14}$, $CONH_2$, $CONHR^{14}$, and $CONR^{14}R^{15}$;

wherein each $R^{13}$ is independently selected from the group consisting of H, $C_1$-$C_6$ alkyl, $C_3$-$C_7$ cycloalkyl, $C_4$-$C_7$ heterocycloalkyl, $CO_2R^{14}$, $CONH_2$, $CONHR^{14}$, $CONR^{14}R^{15}$, $SOR^{14}$, $SO_2R^{14}$, $SO_2NH_2$, $SO_2NHR^{14}$, $SO_2NR^{14}R^{15}$;

wherein each $R^{14}$ is independently selected from the group consisting of H, $C_1$-$C_6$ alkyl, $C_3$-$C_7$ cycloalkyl, $C_4$-$C_7$ heterocycloalkyl, $C_6$-$C_{10}$ aryl, $C_5$-$C_{10}$ membered heteroaryl; said alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl moieties of the foregoing groups are optionally substituted by 1 to 3 substituents independently selected from the group consisting of H, halo, $C_1$-$C_6$ alkyl, CN, $NH_2$, NH $C_1$-$C_6$alkyl, $N(C_1$-$C_6$alkyl$)_2$, O-$C_1$-$C_6$ alkyl; and

wherein each $R^{15}$ is independently selected from the group consisting of H, $C_1$-$C_6$ alkyl, $C_3$-$C_7$ cycloalkyl, $C_4$-$C_7$ heterocycloalkyl, $C_6$-$C_{10}$ aryl, $C_5$-$C_{10}$ membered heteroaryl; said alkyl,

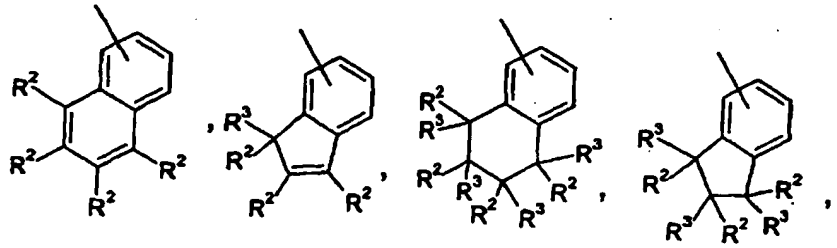
cycloalkyl, heterocycloalkyl, aryl, and heteroaryl moieties of the foregoing groups are optionally substituted by 1 to 3 substituents independently selected from the group consisting of H, halo, $C_1$-$C_6$ alkyl, CN, $NH_2$, NH $C_1$-$C_6$alkyl, N($C_1$-$C_6$alkyl)$_2$, O-$C_1$-$C_6$ alkyl.

2. A compound according to claim 1, wherein E and G are C;

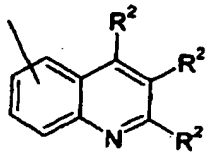
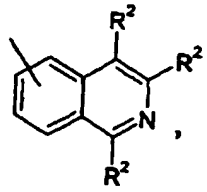
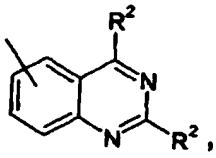
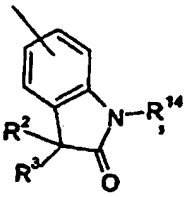
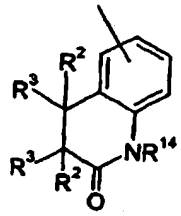
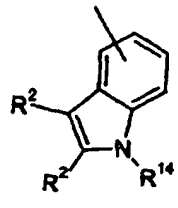
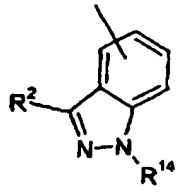
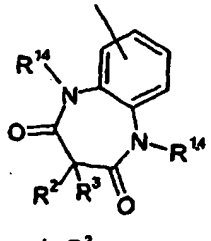
wherein X, W and Q are independently selected from the group consisting of N, $NR^3$, $CR^2$ and $CR^2R^3$; and

wherein Y and Z are independently present or absent, if present Y and Z are selected from the group consisting of N, $NR^3$, $CR^2$ and $CR^2R^3$.

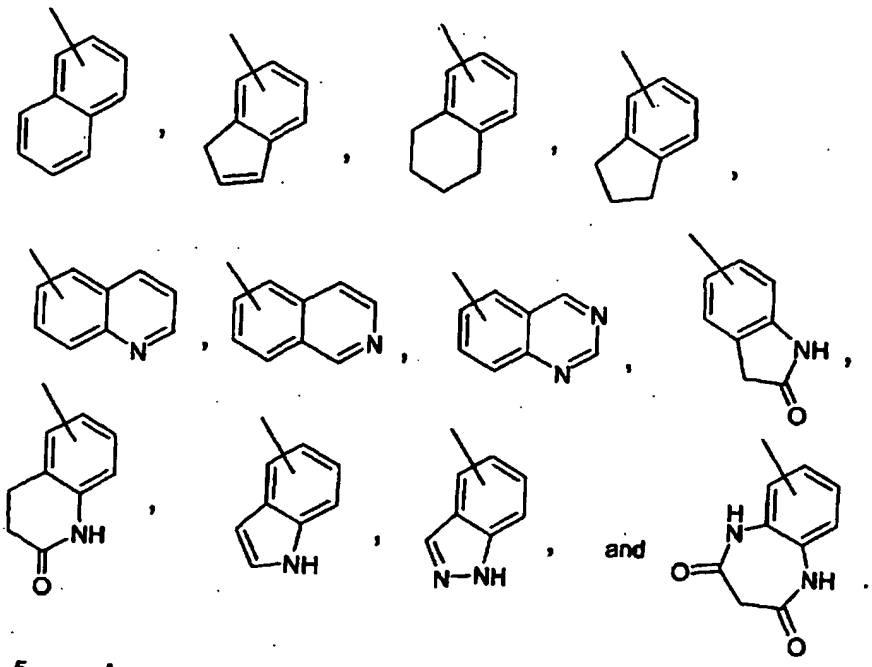
3. A compound according to any of the preceding claims, wherein $R^2$ is selected from the group consisting of:



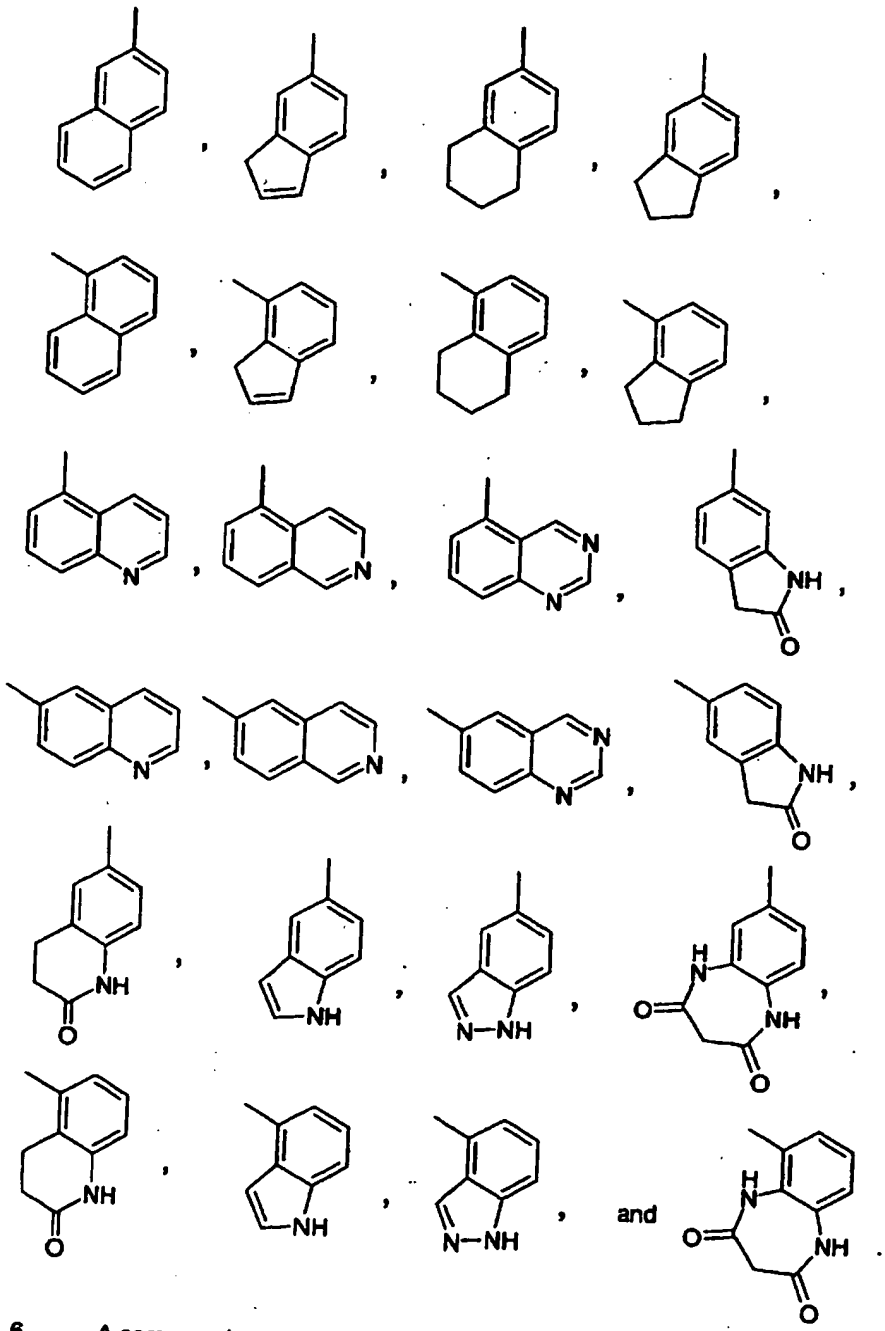


4. A compound according to any of the preceding claims, wherein $R^2$ is selected from the group consisting of:

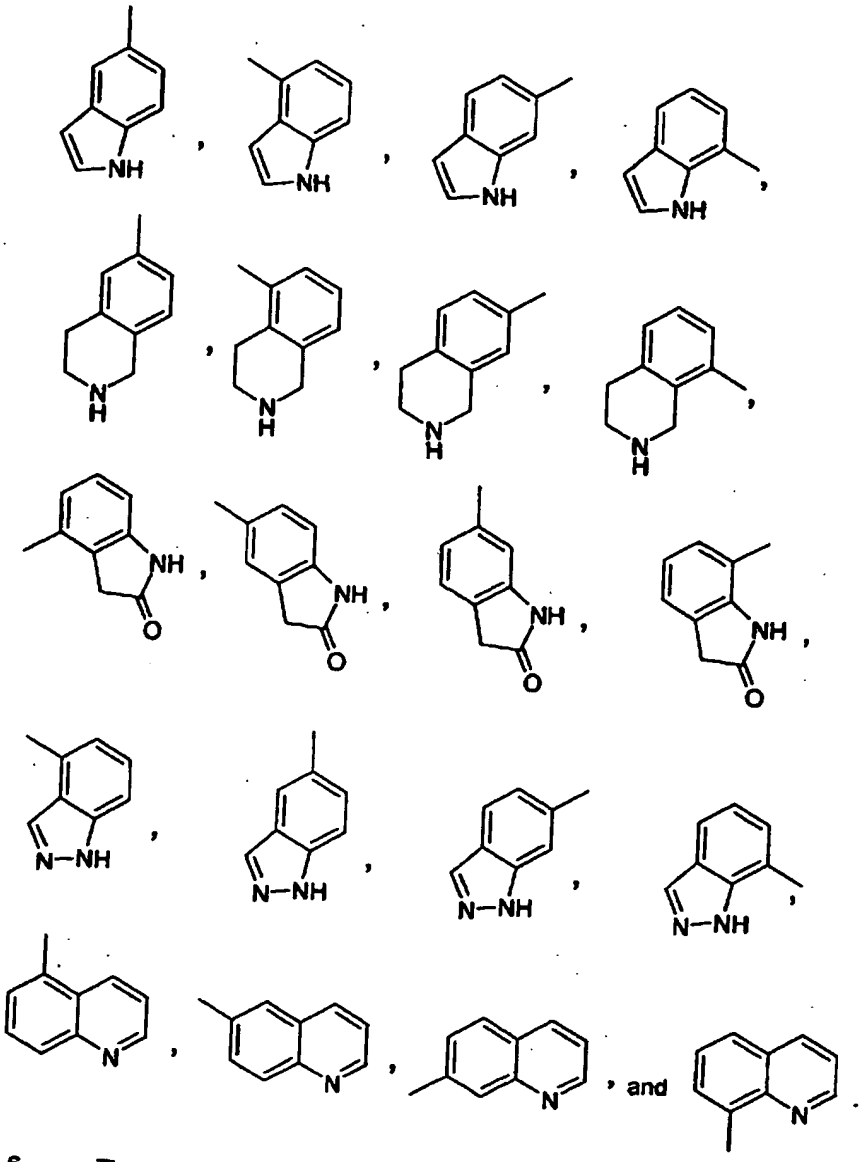


5. A compound according to any of the preceding claims, wherein $R^2$ is selected from the group consisting of:



and

6. A compound according to any of the preceding claims, wherein $R^2$ is selected from the group consisting of:



6. The compound according to any of the preceding claims, wherein wherein A is NH and wherein B is absent.

7. The compound according to any of the preceding claims wherein each $R^2$ is independently selected from the group consisting of H, $C_1$-$C_6$ alkyl, $C_3$-$C_7$ cycloalkyl, $C_4$-$C_7$ heterocycloalkyl, $OC_1$-$C_6$ alkyl, $OC_3$-$C_7$ cycloalkyl, $OC_4$-$C_7$ heterocyloalkyl, $NH_2$, $NHR^6$, $NR^6R^7$, with the proviso that O, N or S atom of the foregoing substituents may not be bound to a carbon atom bound to another heteroatom, said alkyl, cycloalkyl, heterocycloalkyl moieties of the foregoing groups are optionally substituted by 1 to 3 substituents independently selected from the group consisting of H, halo, $C_1$-$C_6$ alkyl, CN, $NH_2$, $NHR^{10}$, $N(R^{10})_2$, $OR^{10}$, $C_1$-$C_6$ alkyl, $C_3$-$C_7$ cycloalkyl, $C_4$-$C_7$ heterocycloalkyl, $CO_2R^{11}$, $CONH_2$, $CONHR^{11}$, and $CONR^{11}R^{12}$; and

wherein each $R^3$ is independently selected from the group consisting of H, $C_1$-$C_6$ alkyl, $C_3$-$C_7$ cycloalkyl, $C_4$-$C_7$ heterocycloalkyl, $CO_2R^6$, $CONH_2$, $CONHR^6$, $CONR^6R^7$ or $R^2$ and $R^3$ taken together with the carbon atom they are linked to can form a 3-7 membered cycloalkyl ring or 4-7 membered heterocycloalkyl ring, wherein each methylene group present in said 3-7 membered cycloalkyl ring and said 4-7 membered heterocycloalkyl ring may be optionally replaced by a C=O group, said alkyl, cycloalkyl, heterocycloalkyl moieties of the foregoing groups are optionally substituted by 1 to 3 substituents independently selected from the group consisting of H, halo, $C_1$-$C_6$ alkyl, CN, $NH_2$, $NHR^{10}$, $N(R^{10})_2$, $OR^{10}$, $C_1$-$C_6$ alkyl, $C_3$-$C_7$ cycloalkyl, $C_4$-$C_7$ heterocycloalkyl, $CO_2R^{11}$, $CONH_2$, $CONHR^{11}$, and $CONR^{11}R^{12}$.

8. The compound according to any of the preceding claims, wherein $R^4$ is selected from the group consisting of H, $C_1$-$C_6$ alkyl, and $C_6$-$C_{10}$ aryl, wherein the alkyl, and aryl moieties of the foregoing groups are optionally substituted by 1 to 3 subsitutents independently selected from the group consisting of H, halo, OH, $NO_2$, $C_1$-$C_6$ alkyl, $C(R^6)=CR^6R^7$, $C\equiv CR^6$, $C_3$-$C_7$ cycloalkyl, $C_4$-$C_7$ heterocycloalkyl, $OC_1$-$C_6$ alkyl, $OC_3$-$C_7$ cycloalkyl, $OC_4$-$C_7$ heterocyloalkyl, C=N-OH, C=N-O($C_1$-$C_6$ alkyl), $NH_2$, $NHR^6$, $NR^6R^7$, $SR^6$, $SOR^6$, $SO_2R^6$, $CO_2R^6$, $CONH_2$, $CONHR^6$, $CONR^6R^7$, $SO_2NH_2$, $SO_2NHR^6$, $SO_2NR^6R^7$, $NHCOR^6$, $NR^6CONR^8$, $NHCONHR^8$, $NR^6CONHR^8$, $NHCONR^6R^7$, $NR^6CONR^6R^7$, $NHSO_2R^6$, $NR^6SO_2R^6$, with the proviso that O, N or S atom of the foregoing substituents may not be bound to a carbon atom bound to another heteroatom.

9. The compound according to any of the preceding claims, wherein $R^5$ is selected from the group consisting of H, Br, Cl, CN, $CF_3$, $CH_2F$, $CHF_2$, $SO_2CH_3$, and $CONH_2$.

10. A compound according to claim 1 selected from the group consisting of:

5-Bromo-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-$N^4$-p-tolyl-pyrimidine-2,4-diamine;

5-Bromo-$N^4$-pyridin-2-yl-N2-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine;

5-Bromo-$N^4$-pyridin-2-ylmethyl-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine;

$N^4$-Benzyl-5-bromo-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine;

5-Bromo-N4-(1R-phenyl-ethyl)-N2-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine;

5-Bromo-$N^4$-(1*rac*-phenyl-ethyl)-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine;

5-Bromo-N4-(1*S*-phenyl-ethyl)-N2-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine;

4-({5-Bromo-2-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-ylamino]-pyrimidin-4-ylamino}-methyl)-benzenesulfonamide

5-Bromo-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-$N^4$-(4-trifluoromethyl-benzyl)-pyrimidine-2,4-diamine;

5-Bromo-$N^4$-(4-methoxy-benzyl)-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine;

5-Bromo-$N^4$-(4-fluoro-benzyl)-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine;

5-Bromo-$N^4$-(3-fluoro-benzyl)-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine;

5-Bromo-$N^4$-naphthalen-1-ylmethyl-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine;

5-Bromo-$N^4$-(4-fluoro-3-trifluoromethyl-benzyl)-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine;

5-Bromo-$N^4$-(3-fluoro-5-trifluoromethyl-benzyl)-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine;

5-Bromo-$N^4$-(4-phenoxy-benzyl)-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine;

5-Bromo-$N^4$-(3,4-difluoro-benzyl)-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine;

5-Bromo-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-$N^4$-(3-trifluoromethoxy-benzyl)-pyrimidine-2,4-diamine;

5-Bromo-$N^4$-(4-chloro-benzyl)-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine;

5-Bromo-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-$N^4$-thiophen-2-ylmethyl-pyrimidine-2,4-diamine;

5-Bromo-N4-furan-2-ylmethyl-N2-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine;

5-Bromo-$N^4$-(2-methyl-benzyl)-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine;

5-Bromo-$N^4$-(3-methyl-benzyl)-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine;

5-Bromo-$N^4$-(4-methyl-benzyl)-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine;

5-Bromo-$N^4$-(2-fluoro-benzyl)-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine;

$N^4$-Biphenyl-2-ylmethyl-5-bromo-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine;

$N^4$-Biphenyl-3-ylmethyl-5-bromo-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine;

5-Bromo-$N^4$-(2-methoxy-benzyl)-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine;

5-Bromo-$N^4$-(3-methoxy-benzyl)-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine;

3-({5-Bromo-2-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-ylamino]-pyrimidin-4-ylamino}-methyl)-N-methyl-benzamide

5-Bromo-$N^4$-(2-chloro-benzyl)-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine;

5-Bromo-$N^4$-phenethyl-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine;

5-Bromo-$N^4$-(2-pyridin-2-yl-ethyl)-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine;

5-Bromo-$N^4$-(2-pyridin-4-yl-ethyl)-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine;

5-Bromo-$N^4$-(2-pyridin-3-yl-ethyl)-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine;

5-Bromo-$N^4$-[2-(3-fluoro-phenyl)-ethyl]-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine;

5-Bromo-$N^4$-(2-phenyl-cyclopropyl)-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine;

5-Bromo-$N^4$-(2-phenyl-cyclopropyl)-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine; (homo-chiral)

5-Bromo-$N^4$-(2-phenyl-cyclopropyl)-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine; (homo-chiral)

5-Bromo-$N^4$-[2-(4-chloro-phenyl)-ethyl]-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine;

5-Bromo-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-$N^4$-(2-thiophen-2-yl-ethyl)-pyrimidine-2,4-diamine;

5-Bromo-$N^4$-[2-(2-fluoro-phenyl)-ethyl]-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine;

5-Bromo-$N^4$-[2-(2-chloro-phenyl)-ethyl]-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine;

5-Bromo-$N^4$-[2-(2-methoxy-phenyl)-ethyl]-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine;

$N^4$-(2-Benzo[1,3]dioxol-5-yl-ethyl)-5-bromo-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine;

5-Bromo-$N^4$-(3-phenyl-propyl)-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine;

5-(5-Bromo-4-phenethylamino-pyrimidin-2-ylamino)-1,3-dihydro-indol-2-one;

5-[5-Bromo-4-(2-chloro-benzylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-(4-Benzylamino-5-bromo-pyrimidin-2-ylamino)-1,3-dihydro-indol-2-one;

5-[5-Bromo-4-(1-phenyl-ethylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-[5-Bromo-4-(3-phenyl-propylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-Bromo-$N^4$-(2-methanesulfonyl-ethyl)-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine;

$N^4$-Benzyl-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine;

$N^4$-Benzyl-$N^4$-methyl-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine;

$N^4$-Methyl-$N^4$-(2-pyridin-2-yl-ethyl)-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine;

[4-(2-Phenyl-morpholin-4-yl)-pyrimidin-2-yl]-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-amine

5-Methyl-$N^4$-(2-pyridin-2-yl-ethyl)-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine;

5-Bromo-$N^2$-(3-piperidin-4-yl-1H-indol-5-yl)-$N^4$-(2-pyridin-2-yl-ethyl)-pyrimidine-2,4-diamine;

5-Bromo-$N^2$-[1-methanesulfonyl-3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-$N^4$-(2-pyridin-2-yl-ethyl)-pyrimidine-2,4-diamine;

5-Bromo-$N^2$-[1-methanesulfonyl-3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-$N^4$-pyridin-2-yl-pyrimidine-2,4-diamine;

5-Bromo-$N^2$-(2-pyridin-2-yl-ethyl)-$N^4$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine;

3-{4-(2-Pyridin-2-yl-ethylamino)-2-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-ylamino]-pyrimidin-5-yl}-acrylic acid; ethyl ester;

5-{5-Bromo-4-[2-(3-chloro-phenyl)-ethylamino]-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-Bromo-$N^4$-[2-(3-chloro-phenyl)-ethyl]-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine;

5-Bromo-$N^4$-[2-(3-chloro-phenyl)-ethyl]-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine;

5-{5-Bromo-4-[2-(4-methoxy-phenyl)-ethylamino]-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-Bromo-$N^4$-[2-(4-methoxy-phenyl)-ethyl]-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine;

5-{5-Bromo-4-[2-(3-methoxy-phenyl)-ethylamino]-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-Bromo-$N^4$-[2-(3-methoxy-phenyl)-ethyl]-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine;

5-[5-Bromo-4-(2-o-tolyl-ethylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-Bromo-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-$N^4$-(2-o-tolyl-ethyl)-pyrimidine-2,4-diamine;

5-[5-Bromo-4-(2-m-tolyl-ethylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-Bromo-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-$N^4$-(2-m-tolyl-ethyl)-pyrimidine-2,4-diamine;

5-[5-Bromo-4-(2-p-tolyl-ethylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-Bromo-$N^2$-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-$N^4$-(2-p-tolyl-ethyl)-pyrimidine-2,4-diamine;

[5-Bromo-2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-pyrimidin-4-ylamino]-acetic acid;

5-{5-Bromo-4-[2-(3-trifluoromethyl-phenyl)-ethylamino]-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-[4-(2-Biphenyl-4-yl-ethylamino)-5-bromo-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-{5-Bromo-4-[2-(3-fluoro-phenyl)-ethylamino]-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-{5-Bromo-4-[2-(2-chloro-phenyl)-ethylamino]-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-{5-Bromo-4-[2-(2-methoxy-phenyl)-ethylamino]-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-{5-Bromo-4-[2-(4-fluoro-phenyl)-ethylamino]-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-{5-Bromo-4-[2-(4-chloro-phenyl)-ethylamino]-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-{5-Bromo-4-[2-(2-fluoro-phenyl)-ethylamino]-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-[5-Bromo-4-(3-phenyl-allylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-{5-Bromo-4-[(thiophen-2-ylmethyl)-amino]-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

6-{5-Bromo-4-[(thiophen-2-ylmethyl)-amino]-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-[5-Bromo-4-(2,3-dimethyl-benzylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

6-[5-Bromo-4-(2,3-dimethyl-benzylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-[5-Bromo-4-(2,5-dimethyl-benzylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

6-[5-Bromo-4-(2,5-dimethyl-benzylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

6-[5-Bromo-4-(2-fluoro-benzylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

6-[5-Bromo-4-(2-trifluoromethoxy-benzylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-[5-Bromo-4-(3-trifluoromethoxy-benzylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

6-[5-Bromo-4-(3-trifluoromethoxy-benzylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-[5-Bromo-4-(4-trifluoromethoxy-benzylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

6-[5-Bromo-4-(4-trifluoromethoxy-benzylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

6-[5-Bromo-4-(2-methoxy-benzylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

6-[5-Bromo-4-(3-methoxy-benzylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

6-[5-Bromo-4-(3-trifluoromethyl-benzylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-[5-Bromo-4-[(thiazol-2-ylmethyl)-amino]-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-[5-Bromo-4-[(5-methanesulfonyl-thiophen-2-ylmethyl)-amino]-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-[5-Bromo-4-(2,3-difluoro-benzylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

6-[5-Bromo-4-(2,3-difluoro-benzylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-[5-Bromo-4-(2,4-difluoro-benzylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

6-[5-Bromo-4-(2,4-difluoro-benzylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

6-[5-Chloro-4-(2-trifluoromethyl-benzylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-Chloro-N2-(1-methyl-1H-indol-5-yl)-N4-(2-trifluoromethyl-benzyl)-pyrimidine-2,4-diamine;

5-Chloro-$N^2$-(1H-indazol-5-yl)-$N^4$-(2-trifluoromethyl-benzyl)-pyrimidine-2,4-diamine;

5-Chloro-$N^2$-(1-methyl-1H-indol-5-yl)-$N^4$-pyridin-2-ylmethyl-pyrimidine-2,4-diamine;

6-{5-Chloro-4-[(pyridin-2-ylmethyl)-amino]-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-Chloro-N2-(1H-indazol-6-yl)-N4-(2-trifluoromethyl-benzyl)-pyrimidine-2,4-diamine;

5-Chloro-N2-(1H-indazol-6-yl)-N4-pyridin-2-ylmethyl-pyrimidine-2,4-diamine;

(5-{5-Bromo-4-[(pyridin-2-ylmethyl)-amino]-pyrimidin-2-ylamino}-indazol-1-yl)-acetic acid; tert-butyl ester;

(6-{5-Bromo-4-[(pyridin-2-ylmethyl)-amino]-pyrimidin-2-ylamino}-indazol-2-yl)-acetic acid; tert-butyl ester;

6-{4-[(Pyridin-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

N2-(1-Methyl-1H-indol-5-yl)-N4-pyridin-2-ylmethyl-5-trifluoromethyl-pyrimidine-2,4-diamine;

(6-{5-Bromo-4-[(pyridin-2-ylmethyl)-amino]-pyrimidin-2-ylamino}-indol-1-yl)-acetic acid; tert-butyl ester;

N4-Pyridin-2-ylmethyl-N2-quinolin-5-yl-5-trifluoromethyl-pyrimidine-2,4-diamine;

2-(6-{5-Bromo-4-[(pyridin-2-ylmethyl)-amino]-pyrimidin-2-ylamino}-indol-1-yl)-N-(2-methoxy-ethyl)-acetamide;

6-{5-Chloro-4-[(3-methyl-pyridin-2-ylmethyl)-amino]-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

(6-{5-Bromo-4-[(pyridin-2-ylmethyl)-amino]-pyrimidin-2-ylamino}-indol-1-yl)-acetic acid;

(6-{5-Bromo-4-[(pyridin-2-ylmethyl)-amino]-pyrimidin-2-ylamino}-indazol-1-yl)-acetic acid; tert-butyl ester;

N2-(1H-Indazol-6-yl)-N4-pyridin-2-ylmethyl-5-trifluoromethyl-pyrimidine-2,4-diamine;

(5-{5-Bromo-4-[(pyridin-2-ylmethyl)-amino]-pyrimidin-2-ylamino}-indol-1-yl)-acetic acid; tert-butyl ester;

(6-{5-Bromo-4-[(pyridin-2-ylmethyl)-amino]-pyrimidin-2-ylamino}-indazol-1-yl)-acetic acid;

(5-{5-Bromo-4-[(pyridin-2-ylmethyl)-amino]-pyrimidin-2-ylamino}-indol-1-yl)-acetic acid;

(5-{5-Bromo-4-[(pyridin-2-ylmethyl)-amino]-pyrimidin-2-ylamino}-indazol-1-yl)-acetic acid;

5-{5-Chloro-4-[(3-methyl-pyridin-2-ylmethyl)-amino]-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-[5-Chloro-4-(3-methanesulfonyl-benzylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

6-[5-Chloro-4-(3-methyl-benzylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-[5-Chloro-4-(2-fluoro-benzylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

6-[5-Chloro-4-(2-fluoro-benzylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-[5-Bromo-4-(2-methoxy-ethylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-[5-Chloro-4-(3-methyl-benzylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

6-{5-Chloro-4-[(4-methyl-pyridin-2-ylmethyl)-amino]-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-(4-Benzylamino-5-chloro-pyrimidin-2-ylamino)-1,3-dihydro-indol-2-one;

5-Bromo-N2-(1H-indol-5-yl)-N4-pyridin-2-ylmethyl-pyrimidine-2,4-diamine;
5-Bromo-N2-(1H-indol-5-yl)-N4-(2-pyridin-2-yl-ethyl)-pyrimidine-2,4-diamine;
5-Bromo-N2-(1H-indol-4-yl)-N4-(2-pyridin-2-yl-ethyl)-pyrimidine-2,4-diamine;
5-Bromo-N2-(1H-indazol-5-yl)-N4-(2-pyridin-2-yl-ethyl)-pyrimidine-2,4-diamine;
5-Bromo-N2-(1H-indazol-6-yl)-N4-(2-pyridin-2-yl-ethyl)-pyrimidine-2,4-diamine;
5-Bromo-N2-(1H-indol-4-yl)-N4-pyridin-2-ylmethyl-pyrimidine-2,4-diamine;
5-Bromo-N2-(1H-indazol-5-yl)-N4-pyridin-2-ylmethyl-pyrimidine-2,4-diamine;
N2-(1H-Indol-5-yl)-N4-pyridin-2-ylmethyl-pyrimidine-2,4-diamine;
N2-(1H-Indazol-6-yl)-N4-pyridin-2-ylmethyl-pyrimidine-2,4-diamine;
N2-(1H-Indol-5-yl)-N4-(2-pyridin-2-yl-ethyl)-pyrimidine-2,4-diamine;
N2-(1H-Indazol-5-yl)-N4-pyridin-2-ylmethyl-pyrimidine-2,4-diamine;
N2-(1H-Indazol-5-yl)-N4-(2-pyridin-2-yl-ethyl)-pyrimidine-2,4-diamine;
N2-(1H-Indazol-6-yl)-N4-(2-pyridin-2-yl-ethyl)-pyrimidine-2,4-diamine;
5-{5-Bromo-4-[(pyridin-2-ylmethyl)-amino]-pyrimidin-2-ylamino}-1,3-dihydro-benzoimidazol-2-one;
5-[5-Bromo-4-(2-pyridin-2-yl-ethylamino)-pyrimidin-2-ylamino]-1,3-dihydro-benzoimidazol-2-one;
5-{4-[(Pyridin-2-ylmethyl)-amino]-pyrimidin-2-ylamino}-1,3-dihydro-benzoimidazol-2-one;
5-[4-(2-Pyridin-2-yl-ethylamino)-pyrimidin-2-ylamino]-1,3-dihydro-benzoimidazol-2-one;
5-Bromo-N2-(1H-indazol-6-yl)-N4-pyridin-2-ylmethyl-pyrimidine-2,4-diamine;
5-{5-Bromo-4-[(pyridin-2-ylmethyl)-amino]-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;
5-[5-Bromo-4-(2-pyridin-2-yl-ethylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;
5-[4-(2-Pyridin-2-yl-ethylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;
5-Bromo-N2-(2-methyl-1H-indol-5-yl)-N4-(2-pyridin-2-yl-ethyl)-pyrimidine-2,4-diamine;
N2-(2-Methyl-1H-indol-5-yl)-N4-pyridin-2-ylmethyl-pyrimidine-2,4-diamine;
N2-(1H-Indol-6-yl)-N4-pyridin-2-ylmethyl-pyrimidine-2,4-diamine;
5-Bromo-N2-(2-methyl-1H-indol-5-yl)-N4-pyridin-2-ylmethyl-pyrimidine-2,4-diamine;
5-Bromo-N2-(1H-indol-6-yl)-N4-pyridin-2-ylmethyl-pyrimidine-2,4-diamine;
5-Bromo-N2-(1H-indol-6-yl)-N4-(2-pyridin-2-yl-ethyl)-pyrimidine2,4-diamine;
N2-(1H-Benzoimidazol-5-yl)-5-bromo-N4-pyridin-2-ylmethyl-pyrimidine-2,4-diamine;
N2-(1H-Benzoimidazol-5-yl)-5-bromo-N4-(2-pyridin-2-yl-ethyl)-pyrimidine-2,4-diamine;
3-[5-Bromo-4-(2-pyridin-2-yl-ethylamino)-pyrimidin-2-yl]-3H-benzoimidazol-5-ylamine
N2-(1H-Benzoimidazol-5-yl)-N4-pyridin-2-ylmethyl-pyrimidine-2,4-diamine;
5-Bromo-N2-(2-methyl-1H-benzoimidazol-5-yl)-N4-pyridin-2-ylmethyl-pyrimidine-2,4-diamine;
N2-(2-Methyl-1H-benzoimidazol-5-yl)-N4-pyridin-2-ylmethyl-pyrimidine-2,4-diamine;

5-Bromo-N2-(2-methyl-1H-benzoimidazol-5-yl)-N4-(2-pyridin-2-yl-ethyl)-pyrimidine-2,4-diamine;

5-Bromo-N2-(2,3-dihydro-1H-indol-5-yl)-N4-(2-pyridin-2-yl-ethyl)-pyrimidine-2,4-diamine;

N2-(2,3-Dihydro-1H-indol-5-yl)-N4-pyridin-2-ylmethyl-pyrimidine-2,4-diamine;

5-Bromo-N2-(1-methyl-1H-indol-5-yl)-N4-(2-pyridin-2-yl-ethyl)-pyrimidine-2,4-diamine;

N2-(1-Methyl-1H-indol-5-yl)-N4-pyridin-2-ylmethyl-pyrimidine-2,4-diamine;

5-Bromo-N2-(2,3-dihydro-1H-indol-5-yl)-N4-pyridin-2-ylmethyl-pyrimidine-2,4-diamine;

5-Bromo-N2-(1-methyl-1H-indol-5-yl)-N4-pyridin-2-ylmethyl-pyrimidine-2,4-diamine;

5-Fluoro-N4-pyridin-2-ylmethyl-N2-quinolin-6-yl-pyrimidine-2,4-diamine;

5-Bromo-N4-pyridin-2-ylmethyl-N2-quinolin-6-yl-pyrimidine-2,4-diamine;

5-Bromo-N2-(1H-indol-7-yl)-N4-(2-pyridin-2-yl-ethyl)-pyrimidine-2,4-diamine;

5-Bromo-N2-(1H-indol-7-yl)-N4-pyridin-2-ylmethyl-pyrimidine-2,4-diamine;

5-Bromo-N2-(1H-indazol-4-yl)-N4-pyridin-2-ylmethyl-pyrimidine-2,4-diamine;

6-{5-Bromo-4-[(pyridin-2-ylmethyl)-amino]-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-Bromo-N2-(1H-indazol-4-yl)-N4-(2-pyridin-2-yl-ethyl)-pyrimidine-2,4-diamine;

5-Bromo-N4-(2-pyridin-2-yl-ethyl)-N2-quinolin-6-yl-pyrimidine-2,4-diamine;

5-Bromo-N4-pyridin-2-ylmethyl-N2-quinolin-5-yl-pyrimidine-2,4-diamine;

5-Bromo-N4-(2-pyridin-2-yl-ethyl)-N2-quinolin-5-yl-pyrimidine-2,4-diamine;

6-[5-Bromo-4-(2-pyridin-2-yl-ethylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-Bromo-N4-pyridin-2-ylmethyl-N2-quinolin-8-yl-pyrimidine-2,4-diamine;

5-Bromo-N4-(2-pyridin-2-yl-ethyl)-N2-quinolin-8-yl-pyrimidine-2,4-diamine;

5-{5-Bromo-4-[(pyridin-2-ylmethyl)-amino]-pyrimidin-2-ylamino}-1H-indole-2-carboxylic acid; ethyl ester;

6-[5-Bromo-4-(2-trifluoromethyl-benzylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-Bromo-N2-(1H-indazol-5-yl)-N4-(2-trifluoromethyl-benzyl)-pyrimidine-2,4-diamine;

5-Bromo-N2-(1H-indazol-6-yl)-N4-(2-trifluoromethyl-benzyl)-pyrimidine-2,4-diamine;

5-Bromo-N2-(1-methyl-1H-indol-5-yl)-N4-(2-trifluoromethyl-benzyl)-pyrimidine-2,4-diamine;

5-Bromo-N2-(1H-indazol-7-yl)-N4-pyridin-2-ylmethyl-pyrimidine-2,4-diamine;

5-Bromo-N2-(1H-indazol-4-yl)-N4-(2-trifluoromethyl-benzyl)-pyrimidine-2,4-diamine;

6-{5-Bromo-4-[(pyridin-2-ylmethyl)-amino]-pyrimidin-2-ylamino}-3H-isobenzofuran-1-one;

N2-Benzothiazol-6-yl-5-bromo-N4-pyridin-2-ylmethyl-pyrimidine-2,4-diamine;

5-{5-Bromo-4-[(pyridin-2-ylmethyl)-amino]-pyrimidin-2-ylamino}-2-methyl-1H-indole-3-carbonitrile

5-Bromo-N4-pyridin-2-ylmethyl-N2-(1-pyridin-2-ylmethyl-1H-indazol-5-yl)-pyrimidine-2,4-diamine;

N2-(1-Benzyl-1H-indol-5-yl)-5-bromo-N4-pyridin-2-ylmethyl-pyrimidine-2,4-diamine;

5-Bromo-N4-pyridin-2-ylmethyl-N2-(1-pyridin-2-ylmethyl-1H-indol-5-yl)-pyrimidine-2,4-diamine;

N2-(1-Benzyl-1H-indazol-5-yl)-5-bromo-N4-pyridin-2-ylmethyl-pyrimidine-2,4-diamine;

5-Bromo-N2-(1-methyl-1H-indazol-5-yl)-N4-pyridin-2-ylmethyl-pyrimidine-2,4-diamine;

5-Bromo-N4-(4-methyl-cyclohexyl)-N2-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine;

5-Bromo-N4-(4-methyl-cyclohexyl)-N2-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine;

5-Bromo-N4-cyclohexylmethyl-N2-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine;

1-{5-Fluoro-4-[(pyridin-2-ylmethyl)-amino]-pyrimidin-2-yl}-3- (1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-ylamine

1-{5-Chloro-4-[(pyridin-2-ylmethyl)-amino]-pyrimidin-2-yl}-3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-ylamine

5-Fluoro-N2-(1H-indazol-5-yl)-N4-pyridin-2-ylmethyl-pyrimidine-2,4-diamine;

5-{5-Fluoro-4-[(pyridin-2-ylmethyl)-amino]-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-Chloro-N2-(1H-indazol-5-yl)-N4-pyridin-2-ylmethyl-pyrimidine-2,4-diamine;

5-{5-Chloro-4-[(pyridin-2-ylmethyl)-amino]-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-Fluoro-N4-(2-pyridin-2-yl-ethyl)-N2-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine;

5-Chloro-N4-(2-pyridin-2-yl-ethyl)-N2-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine;

5-Fluoro-N2-(1H-indazol-5-yl)-N4-(2-pyridin-2-yl-ethyl)-pyrimidine-2,4-diamine;

5-[5-Fluoro-4-(2-pyridin-2-yl-ethylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-Chloro-N2-(1H-indazol-5-yl)-N4-(2-pyridin-2-yl-ethyl)-pyrimidine-2,4-diamine;

5-[5-Chloro-4-(2-pyridin-2-yl-ethylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-{4-[(Pyridin-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-{5-Methoxy-4-[(pyridin-2-ylmethyl)-amino]-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-[5-Methoxy-4-(2-pyridin-2-yl-ethylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-[5-Methoxy-4-(2-trifluoromethyl-benzylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-[5-Bromo-4-[(cyclohex-1-enylmethyl)-amino]-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-[5-Bromo-4-(methyl-pyridin-2-ylmethyl-amino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-[5-Bromo-4-(4-methyl-cyclohexylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-[5-Bromo-4-(4-methyl-cyclohexylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-[5-Bromo-4-(cyclohexylmethyl-amino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-[5-Chloro-4-(2-trifluoromethyl-benzylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

2-(2-Oxo-2,3-dihydro-1H-indol-5-ylamino)-4-[(pyridin-2-ylmethyl)-amino]-pyrimidine-5-carbonitrile

5-[5-Methyl-4-[(pyridin-2-ylmethyl)-amino]-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

N2-(1H-Indazol-5-yl)-5-methyl-N4-pyridin-2-ylmethyl-pyrimidine-2,4-diamine;

5-Fluoro-N4-pyridin-2-ylmethyl-N2-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine;

5-Chloro-N4-pyridin-2-ylmethyl-N2-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine;

2-(2-Oxo-2,3-dihydro-1H-indol-5-ylamino)-4-(2-trifluoromethyl-benzylamino)-pyrimidine-5-carbonitrile

5-{4-[Methyl-(2-pyridin-2-yl-ethyl)-amino]-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-Bromo-N4-cyclohex-1-enylmethyl-N2-[3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyrimidine-2,4-diamine;

N2-(1H-Indazol-5-yl)-N4-pyridin-2-ylmethyl-5-trifluoromethyl-pyrimidine-2,4-diamine;

5-[5-Trifluoromethyl-4-(2-trifluoromethyl-benzylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

6-[2-[(Pyridin-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-4-ylamino]-1,3-dihydro-indol-2-one;

5-[5-Bromo-4-(piperidin-4-ylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-[4-(1-Acetyl-piperidin-4-ylamino)-5-bromo-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

2-(2-Oxo-2,3-dihydro-1H-indol-6-ylamino)-4-[(pyridin-2-ylmethyl)-amino]-pyrimidine-5-carbonitrile

5-{4-[(3-Methyl-pyridin-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

6-{4-[(3-Methyl-pyridin-2-ylmethyl)-amino]-5-trifluoromethyl-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

4-[5-Bromo-2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-pyrimidin-4-ylamino]-piperidine-1-carboxylic acid; tert-butyl ester;

5-[5-Bromo-4-(1-methanesulfonyl-piperidin-4-ylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-[5-Bromo-4-(piperidin-3-ylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

4-[5-Bromo-2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-pyrimidin-4-ylamino]-piperidine-1-carboxylic acid; ethylamide

3-[5-Bromo-2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-pyrimidin-4-ylamino]-piperidine-1-carboxylic acid; ethylamide

5-[4-(1-Benzoyl-piperidin-4-ylamino)-5-bromo-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

6-[4-(3-Methanesulfonyl-benzylamino)-5-methoxy-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

6-[4-(3-Methanesulfonyl-benzylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

6-[4-(3-Methanesulfonyl-benzylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-[4-(1-Benzenesulfonyl-piperidin-4-ylamino)-5-bromo-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-[4-(3-Methanesulfonyl-benzylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

6-{5-Chloro-4-[(piperidin-3-ylmethyl)-amino]-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

6-{5-Chloro-4-[(1-methanesulfonyl-piperidin-3-ylmethyl)-amino]-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

6-{5-Bromo-4-[(piperidin-3-ylmethyl)-amino]-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

6-{5-Bromo-4-[(1-methanesulfonyl-piperidin-3-ylmethyl)-amino]-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

5-[5-Fluoro-4-(3-methanesulfonyl-benzylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one;

5-{5-Bromo-4-[(1-hydroxy-cyclohexylmethyl)-amino]-pyrimidin-2-ylamino}-1,3-dihydro-indol-2-one;

and pharmaceutically acceptable salt, prodrug, hydrate or solvate of the aforementioned compounds.

11. A method for the treatment of abnormal cell growth in a mammal comprising administering to said mammal an amount of a compound of claim 1 that is effective in treating abnormal cell growth.

12. A method according to claim 11 wherein said abnormal cell growth is cancer.

13. A method according to claim 12 wherein said cancer is selected from lung cancer, bone cancer, pancreatic cancer, skin cancer, cancer of the head or neck, cutaneous or intraocular melanoma, uterine cancer, ovarian cancer, rectal cancer, cancer of the anal region, stomach cancer, colon cancer, breast cancer, uterine cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, Hodgkin's Disease, cancer of the esophagus, cancer of the small intestine, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the adrenal gland, sarcoma of soft tissue, cancer of the urethra, cancer of the penis, prostate cancer, chronic or acute leukemia, lymphocytic lymphomas, cancer of the bladder, cancer of the kidney or ureter, renal cell carcinoma, carcinoma of the renal pelvis, neoplasms of the central nervous system (CNS), primary CNS lymphoma, spinal axis tumors, brain stem glioma, pituitary adenoma, or a combination of one or more of the foregoing cancers.

14. A pharmaceutical composition for the treatment of abnormal cell growth in a mammal comprising an amount of a compound of claim 1 that is effective in treating abnormal cell growth, and a pharmaceutically acceptable carrier.

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(71) Applicant (*for all designated States except US*): PFIZER PRODUCTS INC. [US/US]; Eastern Point Road, Groton, CT 06340 (US).

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): KATH, John, Charles [US/US]; Pfizer Global Research and Development, Eastern Point Road, Groton, CT 06340 (US). LUZZIO, Michael, Joseph [US/US]; Pfizer Global Research and Development, Eastern Point Road, Groton, CT 06340 (US).

(74) Agents: LUMB, J., Trevor et al.; c/o Wood, David, J., Pfizer Global Research and Development, UK Patent Department, Ramsgate Road, Sandwich, Kent CT13 9NJ (GB).

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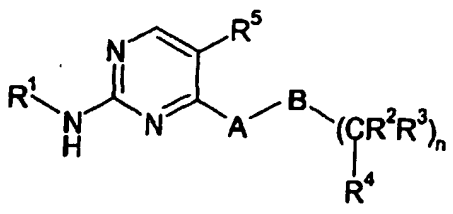
(54) Title: PYRIMIDINE DERIVATES FOR THE TREATMENT OF ABNORMAL CELL GROWTH



(1)

(57) Abstract: The invention relates to compounds of the formula (1) and to pharmaceutically acceptable salts, prodrugs and solvates thereof, wherein $R^1$, $R^2$, $R^3$, $R^4$, $R^5$, n, A and B are as defined herein. The invention also relates to methods of treating abnormal cell growth in mammals by administering the compounds of formula (1) and to pharmaceutical compositions for treating such disorders, which contain the compounds of formula (1). The invention also relates to methods of preparing the compounds of formula (1).

# INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D401/14 C07D407/14 C07D403/12 C07D401/12 A61K31/506
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B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
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Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, EMBASE, BIOSIS, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | WO 02/096888 A (SCHERING AG) 5 December 2002 (2002-12-05) examples 57,156,157,166,259-262 | 1-10,14 |
| X,P | WO 03/032997 A (STEEGMAIER MARTIN ;KRIST BERND (AT); SPEVAK WALTER (AT); SCHOOP AN) 24 April 2003 (2003-04-24) abstract; example 43 | 1,2,7 |
| X,P | WO 03/030909 A (BOYER STEPHEN ; CHEN JIANQING (US); CLARK ROGER B (US); FAN JIANMEI (U) 17 April 2003 (2003-04-17) example 18 | 1-10,14 |

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X,P | WO 03/063794 A (RIGEL PHARMACEUTICALS INC ; ROSSI ALEXANDER B (US); SYLVAIN CATHERINE) 7 August 2003 (2003-08-07) compounds 7.3.211, 7.3.212, 7.3.239, 7.3.733 | 1-10,14 |
| E | WO 2004/046118 A (CHEN GANG ; BRENNAN CATHERINE (US); BIERER DONALD (US); DIXON JULIE (U) 3 June 2004 (2004-06-03) examples 51,53,139,140 | 1-10,14 |
| Y | WO 97/19065 A (CELLTECH THERAPEUTICS LTD ; DAVIS PETER DAVID (GB); MOFFAT DAVID FESTU) 29 May 1997 (1997-05-29) the whole document | 1-14 |
| Y | WO 02/059110 A (GLAXO GROUP LTD ; HARRIS PHILIP ANTHONY (US); MOOK ROBERT ANTHONY (US)) 1 August 2002 (2002-08-01) the whole document | 1-10,14 |
| Y | WO 00/39101 A (BREAULT GLORIA ANNE ; PEASE JANET ELIZABETH (GB); ASTRAZENECA UK LTD () 6 July 2000 (2000-07-06) the whole document | 1-14 |
| Y | WO 00/12485 A (BREAULT GLORIA ANNE ; PEASE JANET ELIZABETH (GB); ZENECA LTD (GB)) 9 March 2000 (2000-03-09) the whole document | 1-14 |
| A | US 5 521 184 A (ZIMMERMANN JUERG) 28 May 1996 (1996-05-28) abstract; claims | 1-10,12 |
| A | KATH J C: "PATENT FOCUS: INHIBITORS OF TUMOUR CELL GROWTH" EXPERT OPINION ON THERAPEUTIC PATENTS, ASHLEY PUBLICATIONS, GB, vol. 10, no. 6, 2000, pages 803-818, XP000919385 ISSN: 1354-3776 the whole document | 1-10,12 |

Form PCT/ISA/210 (continuation of second sheet) (January 2004)

# INTERNATIONAL SEARCH REPORT

... national application No.
PCT/IB 03/06055

**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 11-13 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

Continuation of Box I.1

Although claims 11-13 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

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Continuation of Box I.2

Present claims 1-9,11-14 relate to a disproportionately large number of possible compounds. Support within the meaning of article 6 PCT and disclosure within the meaning of article 5 PCT are to be found, however, for only a small proportion of the componds claimed. In fact, they encompass so many options, alternatives, variables and possible permutations (not mentioning unnecessary redundancies and unexplained provisos) that they appear unclear (and/or too broadly worded) to the extent that a meaningful search of the claims is impossible.

Consequently, the search has been carried out for those parts of the application which do appear to be clear (and/or concise), particularly as recited in the examples and closely related homologous compounds, that is compounds of formula 1 wherein A is NH (cf. claim 7 renumbered - note that the original numbering is erroneous and this claim was as a second claim 6), B is a bond or alkylenyl, R1 is a condensed phenyl linked to the NH group through a carbon atom of the phenyl moiety (cf. claims 3-6 - note the mistypings in these claims wherein R2 should logically read R1) and R4 is a ring (out of about 260 examples largely examplifying a ring, only example 73 represents R4 as H).

The claims also relate to compounds defined by refererence to desirable characteristics or properties, namely prordugs and/or pharmaceutically acceptable salts. The claims cover all compounds having such properties or characteristics, whereas the application provides support within the meaning of article 6 PCT and/or disclosure within the meaning of article 5 PCT for only a very limited number of cases. The claims so lack support , and the application so lacks disclosure, that a meaningful search over the whole claimed scope is impossible. It is noted that here is an attempt made to define the compounds by reference to a result to be achieved which render the scope unclear and exclude the possibility of a meaningful search. Coeespondingly, the search is made as far as prodrugs and pharmaceutically acceptable salts fall in formula 1 (as above limited).

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried

out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.

# INTERNATIONAL SEARCH REPORT

International Application No
PCT/IB 03/06055

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---|---|---|
| WO 02096888 A | 05-12-2002 | DE 10127581 A1 | 02-01-2003 |
| | | DE 10212098 A1 | 23-10-2003 |
| | | BR 0209774 A | 01-06-2004 |
| | | CA 2449118 A1 | 05-12-2002 |
| | | WO 02096888 A1 | 05-12-2002 |
| | | EP 1392662 A1 | 03-03-2004 |
| | | NZ 529654 A | 19-12-2003 |
| | | US 2004102630 A1 | 27-05-2004 |
| WO 03032997 A | 24-04-2003 | CA 2463989 A1 | 24-04-2003 |
| | | WO 03032997 A1 | 24-04-2003 |
| | | EP 1438053 A1 | 21-07-2004 |
| | | US 2003171359 A1 | 11-09-2003 |
| WO 03030909 A | 17-04-2003 | WO 03030909 A1 | 17-04-2003 |
| WO 03063794 A | 07-08-2003 | WO 03063794 A2 | 07-08-2003 |
| | | US 2004029902 A1 | 12-02-2004 |
| | | WO 03063333 A1 | 31-07-2003 |
| | | WO 03061449 A1 | 31-07-2003 |
| | | WO 03063390 A2 | 31-07-2003 |
| | | WO 03063391 A2 | 31-07-2003 |
| | | US 2003137264 A1 | 24-07-2003 |
| | | US 2003137263 A1 | 24-07-2003 |
| | | US 2003142982 A1 | 31-07-2003 |
| | | US 2003170033 A1 | 11-09-2003 |
| | | WO 2004014382 A1 | 19-02-2004 |
| WO 2004046118 A | 03-06-2004 | WO 03095448 A1 | 20-11-2003 |
| | | WO 2004046118 A2 | 03-06-2004 |
| WO 9719065 A | 29-05-1997 | AU 7631496 A | 11-06-1997 |
| | | DE 69627179 D1 | 08-05-2003 |
| | | DE 69627179 T2 | 29-01-2004 |
| | | EP 0862560 A1 | 09-09-1998 |
| | | ES 2195020 T3 | 01-12-2003 |
| | | WO 9719065 A1 | 29-05-1997 |
| | | US 6235746 B1 | 22-05-2001 |
| | | US 5958935 A | 28-09-1999 |
| WO 02059110 A | 01-08-2002 | BR 0116452 A | 30-09-2003 |
| | | CA 2432000 A1 | 01-08-2002 |
| | | CZ 20031748 A3 | 14-04-2004 |
| | | EP 1343782 A1 | 17-09-2003 |
| | | HU 0400691 A2 | 28-07-2004 |
| | | JP 2004517925 T | 17-06-2004 |
| | | NO 20032831 A | 15-08-2003 |
| | | WO 02059110 A1 | 01-08-2002 |
| WO 0039101 A | 06-07-2000 | AU 763091 B2 | 10-07-2003 |
| | | AU 1874300 A | 31-07-2000 |
| | | BR 9916590 A | 23-10-2001 |
| | | CA 2352896 A1 | 06-07-2000 |
| | | CN 1335838 T | 13-02-2002 |
| | | EP 1140860 A1 | 10-10-2001 |
| | | WO 0039101 A1 | 06-07-2000 |
| | | JP 2002533446 T | 08-10-2002 |
| | | NO 20013038 A | 22-08-2001 |

Form PCT/ISA/210 (patent family annex) (January 2004)

# INTERNATIONAL SEARCH REPORT

Int nal Application No
PCT/IB 03/06055

| Patent document cited in search report | Publication date | Patent family member(s) | | Publication date |
|---|---|---|---|---|
| WO 0039101 A | | NZ | 512118 A | 29-08-2003 |
| | | US | 6593326 B1 | 15-07-2003 |
| | | ZA | 200104413 A | 29-08-2002 |
| WO 0012485 A | 09-03-2000 | AU | 5438299 A | 21-03-2000 |
| | | EP | 1107957 A1 | 20-06-2001 |
| | | WO | 0012485 A1 | 09-03-2000 |
| | | JP | 2002523497 T | 30-07-2002 |
| US 5521184 A | 28-05-1996 | AT | 188964 T | 15-02-2000 |
| | | AU | 3569493 A | 07-10-1993 |
| | | BR | 1100739 A3 | 06-06-2000 |
| | | CA | 2093203 A1 | 04-10-1993 |
| | | CN | 1077713 A ,B | 27-10-1993 |
| | | CY | 2229 A | 18-04-2003 |
| | | CZ | 9300560 A3 | 16-02-1994 |
| | | DE | 59309931 D1 | 24-02-2000 |
| | | DK | 564409 T3 | 19-06-2000 |
| | | EP | 0564409 A1 | 06-10-1993 |
| | | ES | 2142857 T3 | 01-05-2000 |
| | | FI | 931458 A | 04-10-1993 |
| | | GR | 3032927 T3 | 31-07-2000 |
| | | HU | 64050 A2 | 29-11-1993 |
| | | IL | 105264 A | 11-04-1999 |
| | | JP | 2706682 B2 | 28-01-1998 |
| | | JP | 6087834 A | 29-03-1994 |
| | | KR | 261366 B1 | 01-08-2000 |
| | | LU | 90908 A9 | 30-04-2003 |
| | | MX | 9301929 A1 | 29-07-1994 |
| | | NL | 300086 I1 | 01-05-2002 |
| | | NO | 931283 A | 04-10-1993 |
| | | NZ | 247299 A | 26-07-1995 |
| | | PT | 564409 T | 30-06-2000 |
| | | RU | 2125992 C1 | 10-02-1999 |
| | | SG | 43859 A1 | 14-11-1997 |
| | | SK | 28093 A3 | 06-04-1994 |
| | | ZA | 9302397 A | 04-10-1993 |
| | | AU | 693804 B2 | 09-07-1998 |
| | | AU | 7697594 A | 01-05-1995 |
| | | CA | 2148477 A1 | 13-04-1995 |
| | | WO | 9509852 A1 | 13-04-1995 |
| | | EP | 0672040 A1 | 20-09-1995 |
| | | JP | 8504834 T | 28-05-1996 |
| | | US | 5543520 A | 06-08-1996 |